Second Edition

DRUGS AND DRUGS

A PRACTICAL GUIDE TO THE SAFE USE OF COMMON DRUGS IN ADULTS

P. Hamilton and D. Hui

Editors: Peter Hamilton and David Hui

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Preface to Second Edition

"There is no medicine like hope, no incentive so great, and no tonic so powerful as expectation of something better tomorrow."

Orison Swett Marden

The second edition of Drugs & Drugs builds on the first edition, with the goal of providing practical, concise and accurate information on commonly used medications in adult medicine.

A number of changes are notable in this edition. The repertoire has now been expanded to include over 90 commonly used classes of medications. We have also revised the original content to make it more practical, and increased the font size for improved readability. Each chapter has been reviewed by both a pharmacist and attending physician to ensure the accuracy of information provided in this manual.

This edition is also released in electronic PDF format. Files for hand-held devices (palm pilots and pocket PCs) will also be released in the near future. Interested users may download the files from http://www.depmed.ualberta.ca/drugs&drugs. We would like to thank Jeffrey Park for his assistance in setting up and maintaining this website, and Dr. Robert Hayward and Dr. Anmol Kapoor for their expertise in perfecting the electronic interface.

We are also grateful to Tanya Hamilton for her artistic design of the covers, Colette Breedevelt and Carrie Hlady for secretarial support, and Dr. Tracey Bryan and Margaret Gray for their assistance in proofreading the entire manuscript and valuable input. We are particularly thankful to Dayle Strachan, Jeff Whissell, and Mark Snaterse from the Department of Pharmacy at the University Hospital for coordinating the pharmacy effort in revising this manual.

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Peter Hamilton, MBBCh, FRCPC (peter.hamilton@ualberta.ca)
David Hui, MD, M.Sc. (medicine_aim@yahoo.ca)
Editors

Preface to First Edition

"Man has an inborn craving for medicine… the desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures."

Sir William Osler (1849 - 1919), Teaching and Thinking, in Adequanimitas, 125

Doctors prescribe drugs. But how well do we know the drugs that we prescribe?

Remember back to the days of pre-clinical years, while we are scrambling to learn the pathophysiology of diseases, the fundamentals of pharmacology is often less emphasized. In the wards, pearls about medication use are only learnt one at a time, and too often forgotten. While there are many textbooks of pharmacology available, they contain pages after pages of detail information, and teasing out the practical bits requires a tremendous amount of time. Handheld-based databases carry good information about drugs, but not the important principles. What we need is a concise drug manual that highlights the clinically important information to help guide prescription in everyday practice.

Drugs & Drugs is a **PRACTICAL** guide consisting of over sixty commonly used medications in adult medicine. Designed to provide students and residents with important **principles, pearls, and pitfalls** of drug use, we hope that Drugs & Drugs can augment clinical practice, and most importantly, enhance patient safety.

Drugs & Drugs represents a collaboration between the Department of Internal Medicine at the University of Alberta and the Pharmacy Department at the University of Alberta Hospital, Capital Health. We would like to take this opportunity to thank the many faculty members, residents, and pharmacists who have contributed their time and effort to the creation of this manual. We are also grateful to Ms. Tanya Hamilton for her artistic design of the covers, and Ms. Carrie Hlady for secretarial support. Funding for printing of this manual is provided by the Dean's fund (FEAC) and the Department of Medicine at the University of Alberta.

This version represents the first edition of Drugs & Drugs. While every effort has been made to ensure the accuracy of information in this manual, there are undoubtedly a number of errors and room for improvement. We welcome any constructive feedback to help make this manual a more practical, comprehensive, and user-friendly resource. A feedback form is included at the end of the manual for your input. Thank you!

Peter Hamilton, MBBCh, FRCPC
David Hui, MD, M.Sc.
Editors

List of Contributors

We would like to thank the following individuals from the Department of Internal Medicine at the University of Alberta and Department of Pharmacy from Capital Health for their time and efforts.

Pharmacy Section Reviewers

Coordinators: Ms. Dayle Strachan, Mr. Jeff Whissell and Mr. Mark Snaterse

Principles of Prescription - Ms. Dayle Strachan and Mr. Jeff Whissell
Analgesics - Mr. Jeff Whissell and Ms. Kirsten George-Phillips
Psychotropic Agents - Mr. Ihor Pecuh and Mr. Kevin Hofstede
Antiepileptics - Ms. Alice Chan
Asthma & COPD Drugs - Mr. Gregg Holowaychuk
Cardiovascular Drugs - Ms. Sheila Walter and Ms. Margaret Ackman
Inotropes & Vasopressors – Ms. Catherine Sych
Lipid Lowering Drugs - Ms. Cindy Polivchuk
Antibiotics & Vaccines - Ms. Alice Chan and Ms. Margaret Gray
Diarrhea & Constipation Drugs - Ms. Melissa Dutchak and Mr. Deon Druteika
Dyspepsia, Peptic Ulcers & Antiemetics - Mr. Ihor Pecuh
Blood Products & Hematinics - Mr. Gregg Holowaychuk
Anticoagulants - Ms. Dayle Strachan
Oral Hypoglycemics - Ms. Cindy Polivchuk
Hormones - Ms. Cindy Polivchuk
Bones & Minerals - Ms. Melissa Dutchak
Fluids & Supplements - Mr. Gregg Holowaychuk and Ms. Catherine Sych
Miscellaneous - Ms. Karen Horon and Mr. Deon Druteika

Chapter Authors & Reviewers

Dr. Alan McMahon
Dr. Albert Yeung
Ms. Alice Chan
Dr. Andrew Lin
Dr. Anmol Kapoor
Dr. Anthony Woods
Dr. Brian Sonnenberg
Dr. Bruce Fisher
Dr. Curtiss Boyington
Dr. David Hui
Dr. Dawna Gilchrist
Ms. Dayle Strachan
Dr. Dennis Kunimoto
Dr. Dominic Carney
Dr. Duncan Webster
Dr. Eric Wong
Dr. Eli Rosenberg
Dr. Fiona Lawson
Dr. Geoff Taylor
Dr. Glen Pearson
Dr. Isabelle Chiu
Mr. Jeff Whissell
Dr. Jennie Johnstone
Dr. Karen Doucette
Dr. Kathy Collinson
Dr. Laurie Mereu
Dr. Loree Larratt
Dr. Lynora Saxinger
Dr. Mao Cheng Lee
Dr. Marc Bibeau
Dr. Marilyn Zeman
Dr. Martina Puchyr
Dr. Mat Rose
Dr. Michael Mant
Dr. Michael McDonald
Dr. Nader Elmayergi
Dr. Noel Gibney
Dr. Peter Hamilton
Dr. Raj Padwal
Dr. Randy Chung
Dr. Roger Tsang
Dr. Ron Damant
Dr. Rshmi Khurana
Dr. Ryan Cooper
Dr. Sabrina Sandhu
Dr. Samuel Asfaha
Dr. Sanjay Kalra
Dr. Sean Van Diepen
Dr. Sharon Watanabe
Dr. Shea Pertman
Dr. Stan Houston
Dr. Stephen Aaron
Dr. Susan Nahirniak
Dr. Syed Ahmed
Dr. Tracey Bryan
Dr. Vijay Daniels
Dr. Vikaash Kumar
Dr. Vincent Thai
Dr. Wendy Sligl
Dr. William Coke
Dr. Winnie Leung
Dr. Winnie Sia
Dr. Winnie Wong

Disclaimer

While dosages are provided for reference purposes, users are STRONGLY RECOMMENDED to consult other resources (CPS, pharmacists, attending physicians) before applying information in this manual for patient care. The Drugs & Drugs Editorial Committee cannot be held responsible for any harm, direct or indirect, caused as a result of application of information contained within this manual.

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PRINCIPLES OF PRESCRIPTION

Pearls, Perils & Pitfalls in Prescribing Drugs

- Type, print or write **legibly**.
- Include the **date** and the **time** of patient orders.
- Write your **name** and **designation**.
  - *Example*: George Washington (student intern) or Dave Barry M.D.
- Always have your orders **counter signed** if you are a medical student.
- Always have your prescriptions **reviewed** if you are prescribing a very toxic drug with which you are not familiar.
  - Chemotherapy must be prescribed only by hematologists and oncologists.
  - Methadone must be prescribed by authorized prescribers only. A temporary license may be obtained.

- If you were about to prescribe a drug that you are unfamiliar with, first learn about the drug from a **reference**.
- Always review a **patient's allergies** to medication before prescribing drugs. When documenting **past adverse drug reactions**, state the nature and severity of reaction.
- Obtain the patient's **medical history** before prescribing, and consider how their history will impact your prescribing decisions.
- When giving a patient a drug ensure they know the following; **what they are taking**, **what it is used for**, **how they should take it**, and **what are the side effects**.
- Always write the **drug name**, **dose**, **route** and **frequency**.

- Consider **reducing the dose** in the presence of **liver, renal or cardiac dysfunction**.
- Always consider **reducing the dose** in the **elderly**. Glomerular filtration rate (GFR) is invariably reduced in the elderly and the serum creatinine will over-estimate the GFR.
- Consider **teratogenicity** of any drugs given to a patient who might be, or could become, pregnant.
  - If the patient **might be pregnant**, confirm with **βhCG** before prescribing.
  - If the patient is **breastfeeding**, review use of the drug in lactation (p. 16).
- Always use the **least toxic alternative**.
  - *Example*: Acetaminophen is generally safer than a non-steroidal anti-inflammatory to treat pain.
- Always ensure that there is a **clear indication** for the drug and that you have considered the potential toxic side effects. What is the risk-benefit ratio?
  - *Example*: gentamicin is associated with significant renal toxicity and ototoxicity. It would be inappropriate to put the patient at risk if there was a safer alternative or if the diagnosis of a serious infection is unlikely.

- **Avoid abbreviations** for drugs (see appendix).
  - *Example*: HCTZ can be read as hydrochlorothiazide or hydrocortisone.
- **Avoid trade names** unless it is a combination drug.
  - *Example*: Dyazide contains hydrochlorothiazide and triamterene.
- **Do NOT use a trailing zero after a decimal point**.
  - *Example*: Morphine sulphate 10.0 mg can be read as 100mg.
- Always use a **leading zero before a decimal point**.
  - *Example*: Digoxin .25 mg should be written as Digoxin 0.25 mg.
- **Avoid open ended prescriptions**.
  - *Example*: Gentamicin 400 mg intravenously daily should be written as *Gentamicin 400 mg intravenously daily for three days and then review*.
- Provide **specific guidelines** when prescribing a dose range.
  - *Example*: For a pain scale <5 give morphine sulphate 10 mg subcutaneous and or a pain scale 6-10 give morphine sulphate 15 mg subcutaneous.

Written by Peter Hamilton; reviewed by Dawna Gilchrist, Dayle Strachan and Jeff Whissell

Principles of Drug Interactions

You will never be able to remember all of the different types of interactions that may occur between pharmaceutical preparations. Practically, it is more useful to concentrate on learning basic principles and a few key drugs and drug classes that are notorious for causing interactions. This list is not meant to be exhaustive.

Basic Principles

- Not all interactions are clinically significant. An interaction is more likely to be clinically significant if:
  - A drug has a narrow therapeutic window.
  - A drug has serious, dose dependent toxicity.
  - The change in serum drug level is at least 30%.
- There are two basic types of interactions:
  - **Pharmacokinetic (what body does to drug)**: occurs with changes to the absorption, distribution, metabolism or excretion of a drug. For example, P-glycoprotein is a membrane transport pump found in many areas of the body including the GI tract, blood brain barrier and kidneys, which limits the distribution of certain drugs into tissues. It acts like a nightclub bouncer, preventing certain drugs from crossing the membrane (i.e. into the bloodstream from the gut or past the blood brain barrier). Inhibition of P-glycoprotein by a drug facilitates the entry of certain drugs into tissues.
  - **Pharmacodynamic (what drug does to body)**: can be thought of as the additive effects of two drugs – e.g. concomitant metoprolol and verapamil therapy will both slow the heart rate.
- There are two major types of drug metabolism (both occur primarily in the liver):
  - **Phase I reactions (cytochrome P450 enzyme system)**: There are over 100 different P450 families and these enzymes are responsible for metabolizing both exogenous and endogenous substances. The major P450 systems involved in drug metabolism are shown in the pie chart below. CYP 3A4 is the most common enzyme system involved in interactions.
  - **Phase II reactions**: acetylation, methylation glucuronidation, sulfation.
- Overall, the goal of drug metabolism is to take a relatively non-polar substance and make it more polar, thus facilitating its excretion in the urine. Phase I reactions will involve exposing an oxygen moiety on the drug molecule (oxidation-reduction type of reaction). Then a Phase II reaction can act on this moiety and, in the process, stick on a polar side group. The drug is then more readily excreted by the kidneys.
- The following are some common medications involved in P450 pathway:
  - **CYP 450 inhibitors:** clarithromycin, erythromycin, protease inhibitors (nelfinavir, ritonavir, indinavir), amiodarone, fluvoxamine, fluoxetine, paroxetine, diltiazem, verapamil, itraconazole, ketoconazole, isoniazid (2C9), fluoroquinolones, quinidine.
  - **CYP 450 inducers:** rifampin, phenobarbital, phenytoin, carbamazepine, isoniazid (2E1).
  - **CYP 450 substrates:** theophylline, amitriptyline, phenytoin, phenobarbital, propafenone, cyclosporine, tacrolimus, clarithromycin, erythromycin, quinidine, alprazolam, diazepam, triazolam, ritonavir, indinavir, saquinavir, amlodipine, nifedipine, felodipine, verapamil, diltiazem, clozapine.

"The true polypharmacy is the skilful combination of remedies."

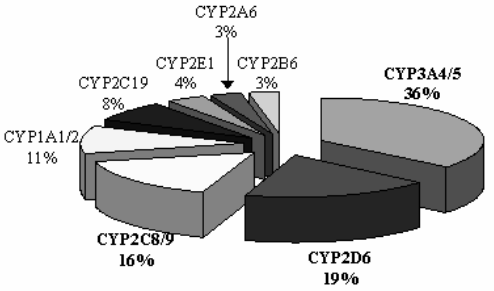
Sir William Osler. The Treatment of Disease. Brit Med J 1909;2:185-9.

Written by Raj Padwal; reviewed by Dawna Gilchrist, Dayle Strachan and Jeff Whissell

Examples of Major Drug Interactions

Initial Drug	Interacting drug(s) or substance	Consequence of Interaction
Absorption		
Calcium channel blockers, cyclosporine	Grapefruit juice	Down regulation of intestinal CYP 3A4 results in higher bioavailability
Tetracyclines	Calcium containing products and foods, fluoroquinolones, phenytoin, levothyroxine	Chelation of drug and decreased absorption
Calcium	Magnesium (and antacids), aluminum (antacids), and iron	Separate by at least 2 hours
Bisphosphonates	Any food	Give at least 1 hour before meals
Cholestyramine and colestipol	Any acidic drugs	Separate by at least 4 hours
Distribution (P-glycoprotein)		
Digoxin	Quinidine, amiodarone, verapamil, diltiazem, spironolactone	Facilitates digoxin absorption and reduces excretion
Metabolism		
CYP 3A4		
Cyclosporine	Diltiazem, verapamil, erythromycin	Inhibition of metabolism with higher serum levels
CYP 2D6		
Codeine	'Caucasian ethnicity'	10% of Caucasians cannot metabolize codeine into its active form (morphine) and will derive no analgesic benefit
Propranolol, metoprolol, tricyclic antidepressants	Quinidine, propafenone or flecainide	Inhibition of metabolism of initial drug, resulting in higher levels
CYP 3A4/2C9		
Warfarin	Erythromycin, amiodarone	Inhibition of metabolism resulting in high INR
Excretion		
Lithium	NSAIDs, diuretics, ACE inhibitors	Decreased excretion and increased renal reabsorption resulting in toxicity
Methotrexate	ASA, NSAIDs	Inhibition of tubular secretion

The Major Cytochrome Enzyme Systems



Principles of Drug Use in the Elderly

Basic

- Seniors comprise 13% of the population but receive 1/3 of the prescriptions.
- Average ambulant senior has 9 to 13 prescriptions filled per year.
- Average ambulant senior is on 5 to 7 prescription and 2 to 4 non-prescription drugs.
- Average nursing home resident is on 7 prescription drugs.
- Seniors are often taking additional drugs, including vitamins and other natural products, that the physician does not know about.

Physiologic Changes in the Elderly

- Decreased liver and renal function
- Decreased lean body mass
- Decreased total body water
- Increased total body fat

Prescribing Practices in the Elderly

- Start low (≤50% of regular starting dose) and go slow regarding drug dosing.
- Use as few drugs as possible - avoid polypharmacy.
- Use as simple a dosing schedule as possible.
- Presenting symptoms may be the result of a prescribed drug.
- Regularly review medications, and stop all unnecessary medications.
- Ensure adherence and consider using compliance packaging (dosette, blister package).
- Dosage adjustments are commonly required and are based on evaluation of renal function, hepatic function, patient's body mass (lean or excess), and alterations in volume of distribution.

High Risk Situations Associated With Adverse Drug Events in the Elderly

- Multiple providers
- Multiple drugs
- Multiple comorbidities
- Living alone
- Cognitive impairment
- Upon discharge from hospital, 40% have medications discontinued, and a 'serious' prescribing error occurs in 22% (Beers. JAGS 1989). Thus, **ALWAYS make sure the patient, their doctor(s), their pharmacist and their caregivers are fully informed, preferably in writing, about all medication changes (doses, deletions, additions) on discharge**.

"One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient."

Frances W. Peabody

Written by Peter Hamilton; reviewed by Fiona Lawson, Dayle Strachan, Jeff Whissell and Dawna Gilchrist

Drugs to Avoid or Use with Caution in Seniors (Revised Beers Criteria)

- **α-agonists**: clonidine (Catapres) has potential for drowsiness, postural hypotension and rebound hypertension on withdrawal.
- **α-blockers**: doxazosin (Cardura) may cause postural hypotension and falls.
- **Anti-cholinergic drugs**: tricyclic anti-depressants (amitriptyline [Elavil], imipramine [Tofranil]) may cause delirium, falls, dry mouth, thirst, tachycardia, hallucinations, glaucoma, pupil dilatation and blurred vision.
- **Anti-psychotic drugs**: can be very useful for treating delirium and managing behavioral problems of dementia. Thus, rather than AVOIDING them, consider judicious use with attention to their potential anticholinergic and extrapyramidal side effects. Each anti-psychotic differs in its relative amount of side effects, dictating the one chosen for the individual patient. N.B. tardive dyskinesia can occur in seniors even with low dose and short term use.
- **Benzodiazepines**: long-acting benzodiazepines such as diazepam (Valium), chlordiazepoxide (Librium), and flurazepam (Dalmane) should be avoided as the half life in the elderly can exceed 80 hours, causing hallucinations, delirium and falls.
- **Digoxin**: use smallest possible dose. Try not to use more than 0.125mg daily. Toxic symptoms may include nausea, headache, visual disturbances, cardiac arrhythmia and sudden death.
- **Diphenhydramine (Benadryl)**: causes sedation and delirium/falls.
- **Meperidine (Demerol) and** propoxyphene (Darvon): toxic metabolites associated with delirium/falls.
- **Non-Steroidal Anti-Inflammatory Drugs and Cox-2 Inhibitors**: adverse symptoms may include GI bleeding, hypertension, stroke, myocardial infarction, renal failure, heart failure, hyperkalemia and delirium. GI bleeding often occurs in the absence of symptoms.
- **Oral Iron**: high dose of ferrous sulphate (>325mg daily) causes constipation with no added benefit.
- **SSRI's**: avoid long term use of fluoxetine (Prozac), paroxetine (Paxil) and others, which may cause SIADH and hyponatremia. In particular, paroxetine is associated with serious anti-cholinergic side effects. Fluoxetine has a very long half life in seniors, and is frequently associated with agitation.
- **Thiazide diuretic**: in high dose >25mg, hyponatremia, hypokalemia and delirium may occur.
- **Others**: amiodarone, amphetamines, barbiturates, muscle relaxants and antispasmodics, nitrofurantoin.

"You can't know all the drugs, but you should be well acquainted with a small number so you are your own personal expert."

David A. Flockhart. ACP Observer 2005.

Written by Peter Hamilton; reviewed by Fiona Lawson, Dayle Strachan, Jeff Whissell and Dawna Gilchrist

Principles of Drug Use During Pregnancy

Basic Principles

- Four questions to ask before prescribing to a pregnant woman.
  1. **Is the medication needed?** Or is the symptom amenable to non-pharmacologic management?
  2. **If the medication is NOT administered**, what are the possible outcomes for mother and/or fetus?
  3. **What data are available on the safety?** Is there another drug with better safety data?
     - Drug safety classifications are not as helpful as a careful consideration of both the potential risks and benefits of a medication for a given clinical situation. Effective older drugs are preferable to recently introduced drugs.
     - **FDA Classification of Pregnancy Risk**
       - **A** Controlled studies show no risk
       - **B** No evidence of risk in humans
       - **C** Risk cannot be ruled out
       - **D** Evidence of risk (but use may still be justified, e.g. anticonvulsants)
       - **X** CONTRAINDICATED in pregnancy (e.g. isotretinoin, warfarin)
     - The teratogenic effect of a drug may vary significantly depending on the **stage of embryonic development** (i.e. "all or none" period from conception to implantation vs. embryonic period (day 18-60) v.s. fetal period). For example, nitrofurantoin and sulfonamides near term may cause hemolytic anemia in infant
  4. **What pharmacokinetic changes of pregnancy may affect the dosing of this drug?**
     - Changes include increased volume of distribution, increased renal clearance, increased hepatic metabolism, and changes in protein binding.
     - Often little data is available, and one may need to monitor levels or effect of drug (e.g. monitor anti-factor Xa levels with low molecular weight heparin).
     - Even after a medication is discontinued, the risk may still exist for several months (e.g. Accutane).
- If using a high risk drug (X class), ensure female patients of reproductive age are counselled to avoid pregnancy and are using at least two methods of birth control.

Websites for Specific Drug Information during Pregnancy

- Micromedex/Reprotox
- Mother's risk: http://www.motherisk.org/
- Briggs

"One of the first duties of the physician is to educate the masses not to take medicines."

Bean WB. Sir William Osler: Aphorisms, 105.

Written by Rshmi Khurana; reviewed by Dawna Gilchrist, Dayle Strachan and Jeff Whissell

Selected Drugs and Teratogenicity

Use justified when indicated	Use justified in some circumstances	Use never justified
Anti-hypertensives		
Methyldopa, labetalol	Nifedipine, beta-blockers (except atenolol), hydralazine, clonidine	Atenolol, ACE inhibitors, ARBs
Anticoagulants		
Unfractionated heparin, most low molecular weight heparins (most data with dalteparin and enoxaparin)[a]		Warfarin
Analgesics		
Acetaminophen	NSAIDs (1st & 2nd trimesters)	NSAIDs (3rd trimester)
Antibiotics		
Penicillins, cephalosporins, metronidazole, clindamycin, acyclovir, erythromycin (except estolate), nitrofurantoin, vancomycin, azithromycin	Trimethoprim, sulfonamides, aminoglycosides[b] (except streptomycin)	Tetracyclines, streptomycin, clarithromycin, fluoroquinolones[c]
GI drugs		
H2 blockers, metoclopramide, dimenhydrinate, sucralfate	Ondansetron, proton pump inhibitors	Misoprostol
Endocrine		
Insulin[d], levothyroxine	Glyburide[e]	Other oral hypoglycemic agents
Asthma		
Inhaled steroids, inhaled β-agonists, systemic steroids, ipratropium, cromolyn, theophylline		Leukotriene inhibitors[f]
Other commonly known teratogens[g]		
Vitamin A (including topical preparations) Alcohol, drugs of abuse Antineoplastics, methotrexate, thalidomide Phenytoin, lithium Iodides, androgens Live vaccines		

[a] Consider monitoring anti-factor Xa levels for therapeutic dosing.
[b] Avoid extended interval dosing (i.e. q24 hour) in pregnancy.
[c] Both clarithromycin and fluoroquinolones show adverse effects in animals.
[d] Effects of glargine unknown; concern regarding increased mitogenicity and affinity to IGF-1 receptors.
[e] One randomized trial of glyburide for use in gestational diabetes in pregnancy showed good outcomes.
[f] Very little human data available.
[g] There are many other terotogens. Always consult a reference and consider risk-benefit ratio before prescribing.

Principles of Drug Use During Lactation

Considerations before prescribing to lactating women

1. Is drug therapy really necessary?
2. If so, the safest drug should be chosen (i.e. acetaminophen instead of ASA).
3. If a drug may present a risk to infant (especially premature infant with altered metabolism), consider measuring blood concentrations in the nursing infant.
4. Drug exposure to the nursing infant may be minimized by taking the medication just after breastfeeding. Alternatively, symptoms may be minimized by giving the medication just before the infant's lengthy sleep period.

Some drugs that are not safe in pregnancy are compatible with lactation (i.e. warfarin, captopril, valproic acid). Conversely, some drugs safe in pregnancy may not be compatible with lactation (i.e. low dose ASA, ranitidine). Always check before prescribing.

Medications		Compatible with lactation (Comments)
Analgesics	Acetaminophen	Yes
	Ibuprofen, Diclofenac	Yes
	ASA	No (small theoretical risk of Reye's syndrome)
	Morphine, Codeine	Yes
Antiemetics/GI	Ranitidine	No
	Omeprazole	No data
	Metoclopramide	No
	Domperidone	Yes (may increase breast milk production)
	Dimenhydrinate	? (watch for infant jitteriness from anticholinergic effects)
Antihypertensives	Labetalol, Methyldopa	Yes
	Nifedipine, Hydralazine	Yes
	Captopril, Enalapril	Yes (data on other ACE-I lacking)
	Metoprolol	Yes (watch for neonatal bradycardia)
	Atenolol	No
	Diuretics	Avoid in first month – may inhibit milk production
Endocrine	Insulin, levothyroxine	Yes
	Oral hypoglycemic agents	No data
	Prophylthiouracil (PTU)	Yes (preferred over methimazole due to lower breast milk excretion)
Anticoagulants	Heparin, LMWHs	Yes
	Warfarin	Yes
Antibiotics	Doxycycline	No
	Quinolones	No data but best avoid
	Most other antibiotics are compatible with lactation (i.e. penicillins, cephalosporins, aminoglycosides, clindamycin, metronidazole etc)	
Psychotropics	Most have unknown effects on the nursing infants	

Drugs to avoid during lactation include antineoplastic/radioactive agents, bromocriptine, cyclosporin, drugs of abuse, ergot alkaloids, gold, iodine-containing compounds, lithium, oral contraceptives.

Websites for Specific Drug Information in Lactation

- Micromedex/Reprotox
- Mother's risk: http://www.motherisk.org/
- Briggs

Written by Winnie Sia; reviewed by Dawna Gilchrist, Dayle Strachan and Jeff Whissell

Principles of Management of Drug Overdose

Early recognition of overdose is essential. This is especially important in the elderly and with accidental overdose. Have a high index of suspicion. A useful resource is the Poison and Drug Information Service (PADIS) poisoning line 1-800-332-1414 (Alberta only).

A. Supportive Care [ABCD]

- **Airway**. Maintain and protect airway as these patients are at risk for respiratory failure and aspiration.
- **Blood pressure**. Treat hypotension. In most cases volume expansion with saline or ringers will suffice. When vasopressor agents are needed, invasive monitoring and consult to ICU/CCU is necessary.
- **Cardiac**. Anticipate and, where appropriate, monitor for arrhythmias.
- **Depression of the CNS**. When coma occurs check blood sugar or give 50ml IV 50% dextrose with thiamine 100mg IV to prevent Wernicke-Korsakoff Syndrome. Where narcotic overdose is suspected, naloxone 2mg IV should be given. However, effect will be temporary only.

B. Prevent Further Drug Absorption

- **Activated charcoal alone** is as good as activated charcoal plus gastric lavage.
- Activated charcoal is effective for most drugs **except** those that are **rapidly absorbed**. e.g. cyanide, strychnine, alcohols and lithium.
- Give 50 to 100g activated charcoal in water immediately. Evidence to show benefit after one hour of intoxication is not available.
- Do **NOT** use activated charcoal when there is a **bowel obstruction, perforation or endoscopy** is contemplated.
- Do **NOT** use emetics such as ipecac as it does not improve outcomes but increases the risk of aspiration.
- Do **NOT** use gastric lavage due to high risk of aspiration.

C. Increased Renal Excretion or Extraction with Hemodialysis or Hemoperfusion

- **Forced alkaline diuresis** will accelerate excretion of acids including ASA and barbiturates.
- Use sodium bicarbonate 44 to 100mmol per litre of half normal saline at 250 to 500ml per hour. **Monitor urine output, volume overload, alkalosis and hypokalemia**. Most patients will require potassium supplements and some will need loop diuretics.
- Consider **hemodialysis** if the patient is very toxic with alcohols, salicylates, theophylline and lithium.

D. Consider Specific Antidotes

- See table.

E. Anticipate Complications

- Delirium, aspiration pneumonia, respiratory failure, electrolyte imbalance, arrhythmias, hypotension, seizures, and others.
- Consider ICU/CCU consultation where appropriate.

Written by Peter Hamilton; reviewed by Dawna Gilchrist, Dayle Strachan and Jeff Whissell

Antidotes and Interventions for Specific Toxins

Toxin	Clinical Syndrome	Antidote/Intervention
Acetaminophen		N-acetylcysteine 150mg/kg (~60ml) in 200ml D5W over 1hr, then 50mg/kg (~20ml) in 500ml D5W over 4hr, then 100mg/kg (~40ml) in 1L D5W over 16hr. Alternatively, N-acetylcysteine 140mg/kg PO/NG, followed by 70mg/kg q4h for 17 doses
Amphetamines	Sympathomimetic	Benzodiazepines
Arsenic/mercury/gold/lead		BAL (dimercaprol)
Benzodiazepines	Sedative/hypnotic	Flumazenil
ß-Blocker	Bradycardia, hypotension	Glucagon, calcium chloride, ventricular pacing
Calcium channel blocker	Bradycardia, hypotension	Calcium, glucagon, ventricular pacing
Carbon monoxide		100% oxygen, hyperbaric oxygen
Cocaine	Sympathomimetic	Benzodiazepines
Warfarin		Vitamin K1, fresh frozen plasma
Cyanide		Nitrites, thiosulfate, hydroxocobalamin
Cyclic antidepressants	Anticholinergic	Blood alkalinization, α-agonist
Digoxin	Dysrhythmias	Digoxin-specific Fab fragments
Ethylene glycol	Sedative/hypnotic	Ethanol, fomepizole, hemodialysis
β-Hydroxybutyrate	Sedative/hypnotic	Respiratory support
Heparin		Protamine sulfate
Hypoglycemic agents		Glucose 50%, octreotide
Iron		Deferoxamine
Isoniazid		Pyridoxine (vitamin B6)
Lithium	CNS alterations	Hemodialysis
Methanol	Sedative/hypnotic	Ethanol, fomepizole, hemodialysis
Opioids	Opioids	Naloxone
Organophosphates/ carbamates	Cholinergic	Atropine, pralidoxime
Salicylates		Urine alkalinization, hemodialysis
Theophylline	Sympathomimetic	Multiple-dose charcoal, hemoperfusion

Adopted with permission from the American College of Physicians MKSAP13, Pulmonary Medicine and Critical Care

Toxic Syndromes Due to Drug Overdose

Clinical Systems	Symptoms
Cholinergic	Salivation, lacrimation, increased urination, bronchorrhea, increased defecation, gastrointestinal upset, emesis, bradycardia, fasciculations, confusion, miosis
Anticholinergic	Dry skin and mucous membranes, hyperthermia, tachycardia, mydriasis, delirium, thirst, urinary retention
Sympathomimetic	Hypertension, tachycardia, seizures, central nervous system excitation, mydriasis, diaphoresis
Narcotic	Miosis, respiratory depression, depressed level of consciousness, hypotension, hypothermia, hyporeflexia
Sedative/hypnotic	Depressed level of consciousness, respiratory depression, hypotension, hyporeflexia, hypothermia

Adopted with permission from the American College of Physicians MKSAP13, Pulmonary Medicine and Critical Care

ANALGESICS

Acetaminophen

Drug Class: antipyretics, analgesics
Drug: **acetaminophen** [Tylenol], **acetaminophen with codeine** [Tylenol #1, #2, #3, #4]

Mechanism of Action & Indications

- Inhibits synthesis of **prostaglandins** in the central nervous system and peripherally, **blocking pain impulse** generation.
- **Antipyretic** action by inhibition of **hypothalamic heat-regulating center**.

Common Dosages

- Acetaminophen 325-650mg PO q4-6h, maximum dose 4g/day
- Acetaminophen extra-strength 500-1000mg PO q4-6h, maximum dose 4g/day

Adverse Effects

- Generally a **well-tolerated medication** with minimal side effects if used appropriately.
- The toxic metabolite **N-acetyl-p-benzoquinoneimine (NAPQI)** is normally inactivated by glutathione (sulfhydryl donor). In the setting of large amount of this toxic metabolite (**≥4g daily**), glutathione conjugation becomes insufficient. NAPQI then binds covalently with cellular macromolecules, causing potential **hepatic cell necrosis** and **acute renal failure**. **N-acetylcysteine**, the antidote, regenerates hepatic glutathione stores.
- **Acute overdose** with a single dose of **>10g** (twenty 500mg tablets) can produce liver injury. **Fulminant hepatic failure** is associated with ingestion >25g.
- **Chronic liver damage** has been reported with long term use in adults of 5-8g/day for several weeks, or 3-4 g/day for one year.

Practical Tips

- For patients with **liver disease/cirrhosis** or **malnutrition**, **limited low-dose therapy** is usually well tolerated. However, hepatotoxicity at dosages <4 g/day have been reported. Avoid chronic use if hepatic impairment or heavy alcohol use.
- Caution in patients with **alcoholic liver disease** (≥3 drinks/day), as this may increase the risk of hepatotoxicity.
- **Metabolized by the liver** and **excreted in urine**. For patients with renal failure, consider dosing interval adjustment as metabolites may accumulate (q6h if creatinine clearance 10-50ml/min, and q8h if creatinine clearance <10ml/min).
- Unlike ASA or NSAIDs, acetaminophen does **NOT** have **anti-inflammatory effect**.
- Acetaminophen is combined with codeine in **Tylenol #1** (300mg/8mg) and **Tylenol #2** (300mg/15mg), **Tylenol #3** (300mg/30mg) and **Tylenol #4** (300mg/60mg) for better pain control. However, in patients with severe pain, the amount of codeine is limited by the maximum dose of acetaminophen. Consider replacing Tylenol #1-4 with acetaminophen plus an opioid (e.g. morphine, codeine) as separate prescriptions.
- Caution in patients with **febrile neutropenia** or **severe infections** as acetaminophen may **mask** the fever, leading to delayed treatment of life-threatening infections. If symptomatic relief needed, consider a **single dose at a time** after fever documented and appropriate actions taken (blood cultures, antibiotics).
- Treatment of **acetaminophen overdose** with N-acetylcysteine: 150mg/kg (~60ml) in 200cc D5W over 1hr, then 50mg/kg (~20ml) in 500cc D5W over 4hr, then 100mg/kg (~40ml) in 1L D5W over 16hr. Alternatively, N-acetylcysteine 140mg/kg PO/NG, followed by 70mg/kg q4h for 17 doses.

Written by David Hui; reviewed by Raj Padwal and Jeff Whissell

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Drug Class: antipyretics, analgesics, anti-inflammatory, anti-platelets

Drugs:

- **ASA**
- **Non-selective NSAIDs—diclofenac** [Voltaren], **ibuprofen** [Advil, Motrin], **indomethacin** [Indocin], **naproxen** [Anaprox, Naprosyn]
- **COX-2 selective NSAIDs—celecoxib** [Celebrex]

Mechanism of Action & Indications

- All act by **inhibition of prostaglandin formation** by cyclooxygenase (COX), which converts the substrate arachidonic acid. **COX-1** is present in **gastric mucosa** and **platelets**, while **COX-2** is present in **inflamed tissue** and the **afferent arteriole of the kidney**.
- For the treatment of mild to moderate **pain** and **fever**. Also for **inflammation** associated with non-infectious causes, usually of MSK origin, but also of pericarditis or pleuritis. Other specific indications include the use of low dose ASA for **platelet inhibition**.

Common Dosages

- Celecoxib 100-200mg PO BID
- Diclofenac 50mg PO BID-TID
- Diclofenac topical 1.5, 2, or 5% apply BID over affected area
- Ibuprofen 300-800mg PO TID-QID
- Indomethacin 25-50mg PO BID-TID

Adverse Effects & Contraindications

- **Gastric ulcer**, **gastritis**, or GI discomfort. The degree of GI side effects varies depending on which class of NSAID drug is used (i.e. indomethacin>ASA>ibuprofen).
- **Hypertension**, **fluid retention**, **renal dysfunction**, interstitial nephritis.
- Impaired platelet function.
- **Hypersensitivity** with angioedema, hives, and bronchospasm.
- Less commonly causes abnormal liver function tests.
- Recent reports of COX-2 selective inhibitors and other NSAIDs increasing **cardiovascular risk**. Use with caution in patients at risk of cardiovascular diseases. Benefits of these agents should to be weighed against the potential adverse effects.
- Contra-indications include:
  - **Hypersensitivity** (ASA sensitivity): severe reactions to one are frequently associated with cross reaction to all NSAIDs, particularly in asthmatics.
  - **Significant renal impairment**, hypertension, or CHF. All may lead to an increase in creatinine, increase in blood pressure, fluid and salt retention, and hyperkalemia, particularly at higher doses.
  - **Active acid peptic disease.**

Practical Tips

- ASA is the prototype. It has unique, **irreversible** effects at low doses on platelets. Other non-specific NSAIDs (diclofenac, naproxen, and indomethacin) have reversible platelet effects. **COX-2** selective inhibitors (celecoxib, valdecoxib) **do not cause platelet inhibition**, and **less risk for gastric ulceration**.
- Topical diclofenac is safer than oral as only a small quantity is systemically absorbed.
- Interactions:
  - May reverse the therapeutic effect of some anti-hypertensive medications (thiazide, β-blockers, ACE inhibitors, ARBs). With **concurrent ACE inhibitor use**, there is also a risk of **hyperkalemia** and **acute renal failure**.
  - Increased risk of **bleeding** with anti-coagulants.
  - Increased risk of lithium toxicity.

Written by Stephen Aaron; reviewed by Raj Padwal and Jeff Whissell

Opioids for Pain Control

Drug Class: analgesics, opioids

Drugs: **buprenorphine** [Subutex, Subutone - partial opioid agonist], **codeine** [Tylenol #1,2,3,4, CodeineContin], **fentanyl** [Duragesic], **hydromorphone** [Dilaudid, HydromorphContin], **meperidine** [Demerol], **methadone**, **morphine** [Statex, MSContin, M-Eslon], **oxycodone** [Percocet-contains acetaminophen, Supeudol, OxyContin], **pentazocine** [Talwin - opioid agonist-antagonist], **propoxyphene** [Darvon – weak opioid agonist]

Mechanism of Action & Indications

- Acts on opioid receptors in the central nervous system.
- For **cancer pain**, the opioids are generally titrated to **achieve significant pain relief with minimal side effects**. For **non-cancer pain**, the opioids are titrated to **achieve optimal function**.

Common Dosages

- Hydromorphone 0.5-1mg SC/IV q4h and hydromorphone 0.5mg IV q1h prn
- Morphine 5-10mg PO q4h and morphine 1mg IV q1h prn

Adverse Effects

- **Central nervous system**: drowsiness, respiratory depression, agitation, vivid dreams, tactile and visual hallucinations, myoclonus, seizures, and hyperalgesia.
- **Gastrointestinal**: constipation, nausea.
- **Genitourinary**: retention of urine (not often).
- **Skin**: cause histamine release with erythema and pruritus.

Practical Tips

- **Stay away from meperidine (Demerol)**. It has high risk of **neurotoxicity** with repeated dosing (due to toxic metabolite) and **anti-cholinergic properties**, thereby leading to confusion or even seizures. Also **avoid partial agonists** as they have greater incidence of side effects and are not as effective as analgesics.
- Opioids should be prescribed on both an **around-the-clock** (q4h for short-acting morphine, hydromorphone and oxycodone) and **q1h prn** basis (for breakthrough pain).
- The hand that prescribes the opioid must also prescribe the **laxative**, as a general rule. Constipation occurs in the majority of patients and generally this side effect will persist as long as the opioid is being used.
- For opioid naïve patients, consider having **metoclopramide** coverage to deal with opioid induced nausea which can be very severe and generally resolves within a week.
- If the patient (e.g. **elderly**) is sensitive to the side effects of the opioid, the dose should be **smaller** and a dose interval of **q6h or q8h** may be needed.
- The dose of parenteral opioids is usually **one-half** of the oral dose. A common mistake is "morphine Xmg PO/SC/IM/IV".
- Long acting opioid preparations are generally not effective for acute pain. Short acting formulations are much better to get a quick response and to allow for rapid titration. Hence, when the existing chronic pain has destabilized or in the presence of **acute moderate to severe pain**, **short acting formulations are superior**.
- Proper use of opioids is generally **not associated with addiction.** Patients' fears should be explored around this issue.
- There is **no ceiling** to the dosages of opioids. Careful **titration** is needed to find a balance between **pain control** and **opioid toxicities**.
- Tylenol #3 does not require a triplicate prescription.

Written by Vincent Thai and Sharon Watanabe; reviewed by Raj Padwal and Jeff Whissell

Advanced Tips

- **Sustained/slow release opioid agents** are **not appropriate for acute or breakthrough pain**. This includes products like fentanyl patches, MS Contin or M-Eslon, and Codeine Contin.
- Therapeutic levels of fentanyl when released from fentanyl patches are only reached after **6 to 12 hours** and steady state may take up to **36 to 48 hours** after the application of the patch. Hence, there is a risk of respiratory depression with the transdermal fentanyl patches if they are titrated too rapidly.
- If the patient is experiencing significant opioid toxicities:
  - Check for precipitating factors such as **dehydration**, **renal failure**, **and infection**.
  - If the pain is well-controlled, consider **decreasing** the dose of opioid.
  - If the dose cannot be decreased due to concerns about pain control, consider switching (**rotating**) the opioid.
- Opioid rotations and equianalgesic ratios (taking **morphine** as **potency of 1**):
  - **Hydromorphone**: **5x** more potent.
  - **Oxycodone**: **1.5x** more potent.
  - **Codeine**: **0.1x** as potent.
  - **Fentanyl**: **10μg** is equivalent to **1mg** of SC morphine (usually given as infusion or as transdermal preparation).
  - **Methadone**: variable depending on the dose of morphine and how long the patient has been on it. Methadone has a longer duration of action than the other opioid agents. Preferably **consult Palliative Care** or the Pain specialist as improper use of methadone can cause respiratory depression and death. Only designated prescribers can prescribe methadone.
    - Note that these equianalgesic ratios are only based on single dose studies. **Clinical judgment** is very important in the final dose calculation. It is customary to **decrease** the dose of the new opioid by approximately **25-30% to account for incomplete cross-tolerance**.
- Even after removal of a transdermal fentanyl patch, the fentanyl is still being released from the subcutaneous tissue at the same rate for the next 8-12 hours. Hence, when **switching from transdermal fentanyl** to another opioid, it is prudent to **wait for at least 8-12 hours** before instituting the new regimen of opioids. The patient can use the breakthrough doses in the meanwhile.
- The same principle applies to the long acting oral formulations of the opioids. e.g. MS Contin will last for about 8-12 hours as well.
- If the patient is using **escalating doses of breakthrough opioids**, you always need to **exclude delirium**.
- Only codeine, morphine and hydromorphone are available in both oral and parenteral form. The preferred route for parenteral opioid administration is subcutaneous, for reasons of comfort and convenience. Fentanyl is only available in parenteral and transdermal preparation. Methadone is available in oral and sometimes rectal formulation, and oxycodone is generally available in the oral formulation.
- Generally, opioids are not CONTRAINDICATED in moderate liver failure. The dose can be **reduced** and the interval **extended** to q4-6h for morphine, oxycodone and hydromorphone.
- In renal failure, the interval can be **extended** to q8h up to even once a day.

"The young physician starts life with twenty drugs for each disease, and the old physician ends life with one drug for twenty diseases."

Bean WB. Sir William Osler: Aphorisms, 122.

Opioids in Addiction

Drug Class: analgesics, opioids

Drugs: **buprenorphine** [Subutex, Subutone - partial opioid agonist], **codeine** [Tylenol #1,2,3,4, CodeineContin], **fentanyl** [Duragesic], **hydromorphone** [Dilaudid, HydromorphContin], **meperidine** [Demerol], **methadone**, **morphine** [Statex, MSContin, M-Eslon], **oxycodone** [Percocet-contains acetaminophen, Supeudol, OxyContin], **pentazocine** [Talwin - opioid agonist-antagonist], **propoxyphene** [Darvon – weak opioid agonist]

Opioid Dependence Disorder (ODD)

- **Opioid addiction**—or more correctly, opioid dependence disorder, is a **medical and psychiatric illness**. Recognition of the signs and symptoms of addiction is essential when prescribing any opioid. "Track marks" indicating IV use of (usually) oral medications, signs and symptoms of opioid withdrawal, multiple doctoring, complaints of inadequate pain relief at higher than expected doses, unusual familiarity with opioid formulations, complaints of pain out of keeping with physical problems, denial of constipation despite regular high-dose opioid use. All these are concerning signs or symptoms and require in-depth exploration.
- When an opioid is appropriately prescribed and taken for **pain relief**, **addiction rarely occurs**. Physical dependence may occur, but the *negative behaviours* associated with an addiction are not encountered.

Signs and Symptoms of Opioid Withdrawal

- **Early**—complaints of generalized pain, aches in joints and muscles, cravings for opioids.
- **Early to moderate**—all the above, plus dilated pupils, sweating, piloerection (goosebumps), rhinorrhea (runny nose), sneezing, yawning, stomach cramps.
- **Moderate to severe:** all the above, plus nausea, vomiting, and diarrhea.
- **Severe**—all the above, plus seizures.

Mechanism of Action & Indications

- Acts on opioid receptors in the central nervous system to produce euphoria (the "high" of opioids) or relief/avoidance of withdrawal symptoms.
- **Methadone** and **buprenorphine** in appropriate dosages prevent all withdrawal signs and symptoms, and reduce or eliminate cravings for use of opioids.
- **Methadone** in appropriate dosages blocks the euphoric effects of other opioids, but **does not block** the analgesic effects of other opioids**.**
- **Buprenorphine** in appropriate dosages blocks the euphoric effects of other opioids, and **may block** the analgesic effects of other opioids.
- Only **methadone** and **buprenorphine** are indicated for the ongoing treatment of opioid dependence disorder. Buprenorphine is rarely prescribed in Canada at present.

Common Dosages

- **Methadone** 60 to 160mg once daily observed (by pharmacist or other healthcare professional) taken by mouth mixed with a non active carrier (such as a flavoured drink, like Tang®). There is no theoretical minimum or maximum dosage of **methadone**.
- **Methadone** in appropriate dosages does not result in significant psychomotor retardation.

Adverse Effects

- **Central nervous system**: drowsiness ("the nod"), respiratory depression, agitation, vivid dreams, tactile and visual hallucinations, myoclonus, seizures, and hyperalgesia.
- **Gastrointestinal**: constipation, nausea.
- **Genitourinary**: retention of urine (not uncommon).
- **Skin**: excessive sweating.
- **Cardiovascular**: doses of methadone in excess of 120mg once daily have been noted to contribute to or cause fatal arrhythmias, presumably through prolongation of the QT interval. All patients on a dose equal to or greater than 120mg per day should have a baseline ECG and be monitored carefully for signs of cardiac destabilization.
- **Drug interactions: methadone** combines *predictably* with other opioids, and *unpredictably* with benzodiazepines, alcohol, tricyclic antidepressants, and barbiturates to increase sedation and respiratory depression, and overdoses occur almost always in the setting of polydrug interactions.

Principals of Treating the Opioid-Dependent Patient

- Control the symptoms of withdrawal
- Treat the intercurrent illnesses
- Treat acute pain appropriately
- Avoid opioid toxicity
- Encourage recognition and treatment of opioid dependence

Practical Tips: The Opioid-Dependent Patient

- Avoid making "value judgments". Addiction is not a lifestyle choice, but a situation in which the patient has lost control over a substance or behaviour.
- Providing dosages of opioids that are inadequate to prevent withdrawal will most often result in the discharge "against medical advice" of these patients. Make note that opioid dependence disorder (ODD) may be an issue, then take practical steps to insure the patient receives the care he requires.
- **Long-acting oral opioids** stabilize serum opioid levels and **prevent withdrawal** symptoms. Most patients with ODD using the oral morphine equivalent of over 300mg/24hr can avoid withdrawal with an oral morphine equivalent of 300mg/24hr; i.e., MSContin/M-Eslon 100mg q8h orally. For people who report a lower daily use, give 75% of the reportedly total daily dose divided q8h, and titrate to eliminate *signs* of withdrawal.
- **Additional opioids** beyond those used to eliminate withdrawal **can be useful in the treatment of acute pain**, but their use should be judicious and titrated to function (i.e., able to go out for a smoke, eating well, clear sensorium). **The goal is pain control, not elimination.** Signs of opioid excess (sedation, confusion, respiratory depression) despite ongoing complaints of pain indicate that the use of opioids for pain control has exceeded its limit. Consultation with a physician knowledgeable in ODD is indicated.
- **Use short-acting oral or parenteral opioids for acute pain**, at approximately twice the usual dose for an opioid-naive patient: e.g., "morphine 5-10mg subcutaneously q3h prn pain, withhold dose if patient shows signs of sedation", or "morphine 25mg orally q3h prn pain, observe dose and confirm ingestion, withhold dose if patient shows signs of sedation".
- **Diversion of oral medications for IV use in hospital occurs.** When in doubt, prescribe parenteral formulations.
- **Patient-controlled analgesia (PCA) is rarely appropriate in this population.** Remember, these individuals have a disorder characterized by *lack of control*.
- **Non-opioid analgesics are effective** for pain relief. Acetaminophen and NSAIDs should be considered where appropriate.
- **Avoid** wherever possible the use of **benzodiazepines** and **barbiturates**.
- **Consult the nursing staff** regarding patient behaviour. The uncooperative and demanding patient who consistently complains of pain may have opioid issues that need to be addressed.

Written by Mat Rose; reviewed by Raj Padwal and Jeff Whissell

Practical Tips: The patient on Methadone

- **Methadone** for the treatment of ODD **is a treatment**, not replacing one addiction with another. Be supportive of the methadone patient, who has made the conscious decision to improve his health and wellbeing.
- Few physicians have an exemption to prescribe methadone for the treatment of ODD. Consult the hospital pharmacists.
- **Methadone once daily** for the treatment of ODD **is not a treatment for pain**.
- **Methadone should be continued**, when it is safe to do so, at the dosage prescribed prior to hospitalization. As a general rule, it should be given orally.
- **Breakthrough doses of methadone should not be used.** Use short-acting opioids for breakthrough pain.
- **No other long-acting opioid analgesic should be prescribed** when the patient is on methadone. Only short-acting opioids should be considered for the relief of acute pain.
- **Non-opioid analgesics are effective** for pain relief. Acetaminophen and NSAIDs should be considered where appropriate.
- **Prior to discharge from hospital**, consult the physician prescribing methadone in the community to arrange resumption of methadone and further analgesic requirements.
- **No prescription for methadone or other opioid outside of hospital** should be given without first consulting the community prescriber.

Advanced Tips

- **Methadone dosage may be split** into three times daily dosing *while in hospital* for provision of longer-acting pain control. The once-daily total dosage should be divided by 3, and rounded up to the nearest 5mg (e.g. Methadone 125mg PO daily observed = Methadone 45mg PO q8h in juice observed). Further increases require consultation with a physician knowledgeable in the treatment of ODD.
- **When acute pain has resolved**, the dosage of methadone can be returned to once-daily (if it has been split), but the dosage should be no higher than that originally prescribed prior to hospitalization (e.g., 125mg daily split to 45mg TID should resume at 125mg daily).
- **Once-daily methadone cannot be resumed safely at previous dosages** when the patient has not received methadone for greater than 3 days. Consultation with a knowledgeable prescriber of methadone for the treatment of ODD is necessary.
- **Standards and guidelines** for methadone maintenance treatment are available through the website of the College of Physicians and Surgeons of Alberta (www.cpsa.ab.ca) and provide more comprehensive guidance, as well as access to resources—including knowledgeable prescribers of methadone—for the physician prescribing for or dealing with the patient on methadone.
- **For patients with known or suspected ODD**, post-hospital prescriptions of any opioid should be left to the family doctor/general practitioner. Short-term, limited amounts of an appropriate opioid analgesic are acceptable. As a general rule, **no more than 3 days worth of an opioid should be prescribed**.

"Medicine hath that virtue, that it never leaveth a man in that state wherein it findeth him; it makes a sick man whole but a whole man sick."

King James I. A Counter Blaste to Tobacco. In English Reprints 1966; 108.

Allopurinol

Drug Class: anti-gout, xanthine oxidase inhibitor

Mechanism of Action & Indications

- **Inhibits xanthine oxidase**, the enzyme responsible for the conversion of hypoxanthine to xanthine to uric acid. Allopurinol is metabolized to oxypurinol, which also inhibits xanthine oxidase. The overall effect is to reduce the plasma and urinary uric acid concentration.
- The main indication is **prevention** of **gout arthritis** and **uric acid nephropathy**. Note that allopurinol is NOT effective for **treatment** of an acute gout attack.
- Also useful for treatment of **secondary hyperuricemia** associated with tumor lysis syndrome and prevention of **recurrent calcium oxalate calculi** in patients with hyperuricosuria.

Common Dosages

- For prophylaxis of gout attacks, allopurinol 100mg PO OD-TID, up to 800 mg/day. Single dose should not exceed 300 mg. Titrate weekly to recommended dosage.
- The average maintenance dosage is 200 to 300 mg/day for patients with mild gout, 400 to 600 mg/day for patients with moderately severe tophaceous gout, and 700 to 800 mg/day in severe conditions.
- For recurrent calcium oxalate stones, allopurinol 100mg PO BID-TID.
- For secondary hyperuricemia associated with chemotherapy, allopurinol 200-300 mg PO BID-TID, starting 1-2 days prior to chemotherapy and continue 2-3 days after chemotherapy. When allopurinol is used with mercaptopurine or azathioprine, the dosage of the latter drugs must be reduced.
- The metabolite of allopurinol, oxypurinol, is renally cleared. Accumulation may lead to severe cutaneous reactions. Thus, allopurinol must be adjusted in renal failure:

CrCl (mL/min)	Usual Dose
100	300 mg daily
80	250 mg daily
60	200 mg daily
40	150 mg daily
20	100 mg daily
10	100 mg every 2 days
Hemodialysis	dose post-hemodialysis or administer 50% supplemental dose

Adverse Effects

- The risk of **exanthematous rash** is as high as 10%, often with concurrent use of ampicillin or amoxicillin. Consider the discontinuation of allopurinol at the first appearance of a rash or other signs of hypersensitivity.
- The incidence of severe cutaneous reactions such as **Stevens Johnson Syndrome or toxic epidermal necrolysis** is greater in renal failure. Thus, it is particularly important to adjust the dose for renal insufficiency.
- **Hypersensitivity reactions** may be increased in patients also on thiazides or ACE inhibitors. When using concurrently, monitor closely for reaction. Loop and thiazide diuretics can increase uric acid levels.
- May cause **renal failure** (through acute tubular necrosis).

Practical Tips

- Due to shifts in uric acid levels, allopurinol can prolong or induce an acute gout attack. **Do not start if a patient is experiencing an acute attack**. Prophylactic **colchicine** 0.6mg BID should be given at the same time when initiating allopurinol.
- Allopurinol may enhance the effect of mercaptopurine, azathioprine, cyclophosphamide, and **oral anticoagulants**.
- **Intravenous treatment** should be considered when oral therapy is not tolerated in **cancer patients** who have elevated uric acid levels and on chemotherapy.

Written by Shea Pertman; reviewed by Raj Padwal and Kirsten George-Phillips

Colchicine

Drug Class: anti-gout

Mechanism of Action & Indications

- Decreases **inflammatory response to urate crystals** by inhibiting leukocyte motility, phagocytosis in joints and lactic acid production. Note that colchicine does not lower uric acid levels.
- Low dose colchicine can be used in the prevention of gout or to prevent an acute attack when starting allopurinol.
- Other less common uses include **pericarditis**, **primary biliary cirrhosis**, and **familial Mediterranean fever**.

Common Dosages

- For treatment of acute gout attacks, colchicine 1.2mg PO q12h until relief or side effects to a maximum of three doses (3.6mg). Wait at least 3 days before initiating another course of therapy.
- For treatment of chronic gout, colchicine 0.6mg oral daily. If pain persists, increase dose to 0.6mg PO BID.
- For pericarditis and primary biliary cirrhosis, colchicine 0.6mg PO BID.

Adverse Effects & Contraindications

- Common side effects include **diarrhea**, nausea, vomiting, and abdominal pain.
- Rare side effects include **rash**, **hypersensitivity reaction**, **bone marrow suppression**, hepatotoxicity, renal failure, myopathy, and peripheral neuritis.
- AVOID in **chronic renal failure**, **anemia**, **leucopenia** and **thrombocytopenia**.

Practical Tips

- A **therapeutic response** in acute monoarticular arthritis to colchicine is **suggestive** but not diagnostic of acute gout.
- **Slow onset of action** from 12 to 48 hours. Therefore loading the dose will **not** hasten the response but will lead to a higher incidence of side effects.
- As colchicine is potentially **marrow toxic**, check CBC at baseline and repeat intermittently if on chronic dosing. Advise your patients of the potential side effects. Ask them to report **persistent or unexplained fever** and **immediately stop taking colchicine** should they develop symptoms suggestive of neutropenia (e.g. febrile illness).
- Dosing of colchicine is primarily limited by **GI symptoms**.
- **Intravenous colchicine** is **NOT** recommended as:
  - Colchicine is **absorbed well orally** and therefore IV dosing not necessary.
  - Intravenous form is associated with a **higher incidence** of local irritation, thrombophlebitis, and bone marrow toxicity.
- Dose should be reduced by **50%** in patients with creatinine clearance of **10-50ml/min**. Do not use in patients with creatinine clearance < 10mL/min.

"Poisons and medicines are oftentimes the same substances given with different intents."

Peter Mere Latham. The Collected Works of Dr. P.M. Latham 1878.

Written by Shea Pertman; reviewed by Peter Hamilton and Kirsten George-Phillips

PSYCHOTROPIC AGENTS

Atypical Antipsychotics

Drug Class: antipsychotic agents, so named because they are supposed to cause a lower incidence of extrapyramidal side effects with similar antipsychotic efficacy.

Drugs: **aripiprazole** [Abilify], **clozapine** [Clozaril], **olanzapine** [Zyprexa], **quetiapine** [Seroquel], **risperidone** [Risperdal], **ziprasidone** [Geodon]

Mechanism of Action

- **D2 receptor antagonists** (weaker than typical antipsychotics) and **serotonin 5H2 receptor antagonists**.
- In addition to treatment of **psychotic disorders**, may also be used for management of **agitation**.

Common Dosages

- Olanzapine 5mg PO daily, also available as quick dissolve
- Quetiapine 25mg BID-TID
- Risperidone 0.5mg PO BID, also available as quick dissolve

Adverse Effects

- Purportedly **lower incidence of extrapyramidal side effects** (dystonia, akathisia, bradykinesia, dyskinesia) than typical antipsychotics.
- Significant side effects include **neuroleptic malignant syndrome**, **tardive dyskinesia**, **sedation** (histamine blockade), **orthostatic hypotension** (alpha receptor blockade), and **hyperprolactinemia** (dopamine blockade, mainly risperidone).
- Major additional side effect is an association with **weight gain**, development of **type 2 diabetes** and **dyslipidemia**. Case reports of precipitation of DKA have also been published.
- Clozapine can cause **agranulocytosis**. Periodic monitoring of blood counts is warranted. Lab results need to be sent to drug manufacturers on a regular basis for clozapine to be dispensed.
- **Prolonged QT** with torsades de pointes with the use of risperidone.
- **Anticholinergic side effects** (dry mouth, blurred vision, constipation, confusion, urinary retention, and tachycardia) are infrequent.

Practical Tips

- Studies showing a **decrease in extrapyramidal side effects** have been done in **younger**, **schizophrenic populations** and have been extrapolated to elderly populations.
- Clinical experience with **aripiprazole** and **ziprasidone** is more limited as both drugs are **not available in Canada** yet. They are better for negative symptoms than typicals, and are less likely to cause movement disorders. In addition, they have not been associated with weight gain and diabetes risk. Ziprasidone causes a higher incidence of QT prolongation compared to other agents.

> *"Half of the modern drugs could well be thrown out of the window, except that the birds might eat them."*
>
> *Dr. Martin Henry Fischer*

Written by Raj Padwal; reviewed by Peter Hamilton, Kathleen Collinson and Ihor Pecuh

Benzodiazepines

Drug Class: anticonvulsants, anxiolytics, sedatives, and hypnotics

Drugs:

- **Anti-seizure activity—clonazepam** [Rivotril], **clobazam** [Frisium], **diazepam** [Valium], **lorazepam** [Ativan]
- **Anxiolytic activity—alprazolam** [Alprax], **lorazepam** [Ativan], **clonazepam** [Rivotril], **diazepam** [Valium]
- **Hypnotic activity—oxazepam** [Serax], **temazepam** [Restoril], **triazolam** (short-term use only; rebound insomnia, anterograde amnesia), **flurazepam** (long half-life with hangover effect; care in elderly), **nitrazepam** (long half-life → hangover effect; care in elderly)
- **Others—midazolam** [Versed], **bromazepam** [Lectopam], **chloridiazepoxide**, **chlorazepate**

Mechanism of Action & Indications

- Potentiate the effects of **gamma-aminobutyrate** (GABA), the major inhibitory neurotransmitter in the CNS, and **other inhibitory transmitters** by binding to specific benzodiazepine receptor sites. It is believed there are different types of benzodiazepine receptors in different areas of the CNS that produce the various pharmacologic actions of the agents.
- Used as **anxiolytics**, **hypnotics**, management of **alcohol withdrawal**, **anticonvulsants**, **skeletal muscle relaxants**, **conscious sedation**, **surgical adjuncts** such as perioperative anxiolysis/sedation, and induction and maintenance of **anesthesia**.

Common Dosages (NOTE: DOSES need to be reduced in the elderly)

- Lorazepam 0.5-1mg PO/SL qhs for sleep
- Lorazepam 1mg SL/IV q5min prn for seizures/alcohol withdrawal
- Midazolam 0.5-2mg IV as initial dose for conscious sedation. Additional doses may be titrated over at least 2 minute increments to a maximum dose of 5 mg
- Diazepam 2-10mg PO/IV BID-QID
- Clonazepam 0.25-0.5mg PO BID-TID
- Oxazepam 10-30mg PO TID-QID

Adverse Effects & Contradictions

- Common side effects include **drowsiness**, **dizziness**, **ataxia**, **CNS depression**, **psychomotor impairment**, **confusion**, **cognitive impairment**, aggression, increased risk of **fall/fracture** (especially in elderly), and anterograde amnesia.
- **Tolerance** and **dependence** may develop.
- Benzodiazepine **withdrawal**
  - Depends on **duration** of therapy, **dose**, **rate of taper**, and **half-life of benzodiazepine**. Onset usually **within 1-2 days** for **short-acting** benzodiazepines, and **3-8 days** for **long-acting** forms.
  - Symptoms include **insomnia**, **nausea and vomiting**, **twitching**, **irritability**, **anxiety**, paresthesias, tinnitus, **delirium**, and **seizures**.
  - To prevent withdrawal, pay particular attention when discontinuing benzodiazepines. Dose reductions should be titrated against symptoms of withdrawal.
    - Substitute an **equivalent dose of a long-acting benzodiazepine** (clonazepam/diazepam/chlordiazepoxide), then taper slowly over 4-12 weeks, OR
    - Initially **reduce** the dose of the agent by **25%**, and proceed with **further reductions** of **10-15%** of the remaining dose every 4 to 7 days.
    - Take care when tapering last 25% of the dose, as this is often when withdrawal will occur. Go slowly.

- Benzodiazepine **overdose**
  - Most benzodiazepines have a **wide therapeutic index**.
  - **Flumazenil** is a benzodiazepine antagonist that can be used to treat benzodiazepine overdose; however, it has a short half-life and continuous monitoring is required. Use with care in multiple overdose.
- Particular caution in patients with a history of **substance abuse**, **sleep apnea**, **cognitive disorder**, **renal disease**, **acute narrow-angle glaucoma**, **porphyria**, **depression**, **myasthenia**, and **pregnancy**.
- Caution when using **benzodiazepine and opioids** together, as the risk of **respiratory depression** can be increased significantly.
- Avoid use in **elderly** as much increased risk of **falls**, **motor incoordination**, **cognitive impairment**, **sedation**, **hangover effect**, and **dependence**. If use is necessary, avoid agents with long half lives and use lower doses (start at ¼ to ½ of normal starting dose).

Practical Tips

- The more **lipophilic** agents have the **quickest** absorption and **onset** of clinical effect (i.e. diazepam).
- **Short to intermediate acting agents** include alprazolam, bromazepam, lorazepam, oxazepam, temazepam, and triazolam. **Long acting agents** include chloridiazepoxide, clonazepam, chlorazepate, diazepam, flurazepam, and nitrazepam.
- Oxazepam, lorazepam, and temazepam undergo **glucuronide conjugation** and the half lives of these agents are only slightly altered in the presence of hepatic dysfunction. Therefore, they could be considered the **drugs of choice in patients with liver disease**. Other benzodiazepines may be used, but the dosage or dosing interval needs to be altered to compensate for impaired hepatic metabolism (those benzodiazepines undergoing oxidation and those with long half lives).
- Diazepam, chlorazepate, chloridiazepoxide, and flurazepam have **active metabolites with very long half-lives**, and **cumulative effects occur with chronic administration**.
- Drug interactions include:
  - Increased **CNS depression** with **antidepressants**, **antihistamines**, **barbiturates**, **ethanol** and **opioids**.
  - Increased benzodiazepine levels with concurrent use of allopurinol, oral contraceptives, ketoconazole, estrogen, cimetidine, erythromycin, fluoxetine, isoniazid, omeprazole, valproic acid, and grapefruit juice.
  - Decreased benzodiazepine levels by carbamazepine, phenobarbital, rifampin, and smoking.
  - Benzodiazepines may increase levels of digoxin and phenytoin.
  - Diazepam (partially), alprazolam, clonazepam, triazolam are **metabolized by CYP3A4**. Thus, beware of inducers and inhibitors of this hepatic enzyme.

"Imperative drugging—the order of medicine in any and every malady—is no longer regarded as the chief function of the doctor."

Sir William Osler. Medicine in the Nineteenth Century, in Aequanimitas, 254.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Drug Class: anti-depressants

Drugs: **fluoxetine** [Prozac], **sertraline** [Zoloft], **paroxetine** [Paxil], **fluvoxamine** [Luvox], **citalopram** [Celexa]

Mechanism of Action & Indications

- By **blocking** the action of the **presynaptic serotonin reuptake pump**, both the amount of serotonin in the synapse as well as postsynaptic serotonin receptor occupancy increase leading to **increased serotonergic activity**.
- Reduce symptoms of **depression**, **obsessive ruminations**, and **anxiety** (generalized anxiety, social anxiety, panic, and post-traumatic stress disorders), as well as **bulimia nervosa**, **seasonal affective disorder**, and **premenstrual dysphoric disorder**.

Common Dosages

- Fluoxetine 20-80mg PO daily (usual effective dose is 20mg)
- Sertraline 25-200mg PO daily (usually started at 50mg, effective maintenance dose typically 50-100mg)
- Paroxetine 10-60mg PO daily (usual starting and maintenance dose is 20mg)
- Fluvoxamine 50-300mg PO daily divided into 2 doses (usual starting dose is 50 mg daily; therapeutic dose 150-250 mg)
- Citalopram 20-40mg PO daily (usual starting dose 20mg)
- Escitalopram 10-20mg PO daily

Adverse Effects & Contraindications

- May cause **sexual dysfunction**, **insomnia**, **nausea**, **diarrhea**, **anxiety**, **dry mouth**, or **mild fatigue**. Most side effects usually present at the start of treatment and tend to resolve over 1-2 weeks.
- **Sexual dysfunction**: reduced libido in men and women, anorgasmia in women, and increased ejaculation latency in men. Sexual dysfunction may persist during treatment.
- **Bleeding**: a decrease in intraplatelet serotonin concentrations may affect platelet aggregation causing an increased risk of GI bleeding, particularly in patients concurrently taking NSAIDS. SSRIs may increase the need for transfusions with surgery.
- **SIADH** may occur with higher risk in the elderly.
- **Suicide risk**: no compelling evidence indicating SSRIs or newer antidepressants increase the risk of suicidal ideation or completed suicide in adults. May cause small increase to the risk of non-fatal self-harm compared with placebo.
- **Co-administration of monoamine oxidase inhibitors (MAOI)** is CONTRAINDICATED. Potential for producing a **potentially lethal serotonin syndrome** (characterized by nausea, vomiting, flushing, agitation, hyperthermia, diaphoresis, tachycardia, autonomic instability, tremor, hyperreflexia, myoclonus, and rigidity) due to dangerously high levels of brain serotonin.

Practical Tips

- The antidepressant effects of SSRIs may not appear until **3 to 6 weeks after initiation** of treatment.
- The **overall efficacy** of the various SSRIs appears to be **similar**, though they differ in potency, receptor selectivity, and pharmacokinetic properties. These differences determine the side-effect profile and interactions with other medications, and help guide the choice of an appropriate SSRI for a particular patient.
- After **2 weeks** of treatment with fluoxetine, **over half** of eventual responders show a **response**. Approximately 80% of those who do not respond by 4-6 weeks do not have a response at 8 weeks.

Written by Eli Rosenberg; reviewed by Kathleen Collinson

- To minimize occurrence of discontinuation syndromes, all antidepressants should be slowly **tapered (25% dose reduction per week)**, rather than abruptly discontinued. Within days of abrupt cessation, patients may suffer from dizziness, nausea, fatigue, muscle aches, chills, anxiety, and irritability. While not dangerous, discontinuation side effects can be distressing and uncomfortable, often lasting 1-2 weeks.
- All SSRIs are **hepatically metabolized**, are relatively safe in overdose, and have relatively little affinity for histaminic, dopaminergic, alpha-adrenergic, and cholinergic receptors.

"When I was a boy, [the] doctor…examined me gravely, asked questions that were searching [and] retired…. [He] emerged with a bottle from which he instructed me to drink three times a day…. I regarded the doctor as a magician…. My adult life my various doctors have given me medicine--it tends to be in pill form nowadays--which plainly comes from a pharmaceutical company, and I leave his office thinking of him as a middleman between me and a large pill works. He has lost his magic."

Robertson Davies 1984

Typical Antipsychotics

Drugs: **chlorpromazine** [Largactil], **fluphenazine** [Modecate], **flupenthixol** [fluanxol], **haloperidol** [Haldol], **loxapine** [Loxapac], **methotrimeprazine** [Nozinan], **perphenazine** [Trilafon], **pimozide** [Orap], **trifluoperazine** [Stelazine], **zuclopenthixol** [Clopixol]

Mechanism of Action & Indications

- Act centrally, exhibiting a high affinity for **blocking postsynaptic mesolimbic dopamine (D2) receptors**, and to a lesser extent, D1 receptors.
- In addition to their role as **antipsychotic agents** for the treatment of positive symptoms in schizophrenia, they are also used to treat **agitation, impulsivity, aggression, bipolar disorder and tourettes**.
- Some agents have also been used for treatment of **nausea and vomiting and for night-time sedation**.

Common Dosages

- For agitation/delirium
  - Haloperidol 1-4mg PO/IV/IM/SC q4-6h prn
  - Loxapine 2.5mg PO/IM/SC q6-8h prn
- For psychiatric indications
  - Chlorpromazine 50-1000mg PO total daily dose (div BID-QID)
  - Fluphenazine Decanoate 25-100mg IM q2-4 weeks
  - Flupenthixol 3-12mg PO total daily dose (div q6-8h)
  - Flupenthixol Decanoate 25-200mg IM q2-4 weeks
  - Haloperidol 2-20mg PO total daily dose (div BID-TID)
  - Haloperidol Decanoate 50-200mg IM q2-4 weeks
  - Loxapine 50-100mg PO/IM total daily dose (div BID)
  - Methotrimeprazine 25-100mg total daily dose (div BID-TID)
  - Perphanzine 12-64mg PO total daily dose (div BID-QID)
  - Pimozide 2-16mg PO total daily dose (div daily-BID)
  - Trifluoperazine 10-40mg PO total daily dose (div BID)
  - Zuclopenthixol 10-60mg PO total daily dose (div BID-TID)
  - Zuclopenthixol Acetate 50-150mg IM q2-3 days
  - Zuclopenthixol Decanoate 100-300mg IM q2–4 weeks

Adverse Effects & Contraindications

- The likelihood of certain adverse effects occurring is directly related to the potency of the antipsychotic. It is a relationship where the higher potency agents (lower mg dose), bind more tightly to the dopamine D2 receptors. The **higher the potency** the more likely the agent is to cause neurological side effects. The **lower the potency** the more likely the agent is to cause the non-neurological side effects. The order of potency from highest potency to lowest potency is: pimozide > haloperidol > fluphenazine > flupenthixol > trifluoperazine > perphenazine > loxapine > zuclopenthixol > methotrimeprazine > chlorpromazine.
- Neurological side effects:
  - **Tardive dyskinesia (TD)**: involuntary movements of the face, lips, jaw, tongue, eyes, limbs, trunk, neck and respiratory system. Increasing the dose of the agent only masks symptoms and will worsen TD in the future. Risk increases with prolonged use of high potencies. Treatments include vitamin E, tetrabenazine and clozapine.
  - **Dystonia**: torsions and spasms of muscle groups. Occurs within 5 days of initiation or dose increase. Prevent by using lowest possible dose and slow titration. Treat with benztropine or diphenhydramine IM.
  - **Akathisia**: motor restlessness which manifests itself in fidgeting, pacing and rocking. Occurs within 10 days of initiation or increase in dose. Treat by reducing dose or switch to lower potency agent. Add for the short term benzodiazepines or beta-blockers.

Written by Jeff Whissell; reviewed by Raj Padwal, Kathleen Collinson and Kevin Hofstede

- **Parkinsonism**: stiffness, shuffling, mask-like face, pill-rolling tremor, cogwheel rigidity, stooped posture, micrographia, bradykinesia, drooling and postural instability. Traditional anti-parkinson medications are ineffective. Onset occurs with 30 days of initiation or dose increase. Treat with a dose reduction or switch to lower potency agent. Add benztropine, procyclidine, or trihexyphenidyl for short term.
- **Neuroleptic malignant syndrome (NMS)**: a serious metabolic syndrome characterized by symptoms of muscle rigidity, tachycardia, hyperthermia, autonomic dysfunction and altered consciousness. Stop medication immediately and institute supportive treatment. Dantrolene and bromocryptine are given.

- Non-Neurological side effects:
  - **Drowsiness and sedation**
  - **Syncope**: due to hypotension
  - **Anticholinergic side effects**: constipation, dry mucous membranes (eyes, nose, mouth), blurred vision, and urinary retention.
  - **Prolactin elevation and sexual dysfunction**: decreased libido, erectile dysfunction, ejaculatory dysfunction, priapism, gynecomastia, galactorrhea and menstrual irregularities.
  - **Gastrointestinal effects**: weight gain due to increased appetite, dysphagia, dyspepsia and sialorrhea.
- Rare and important side effects:
  - **Central nervous system**: seizures.
  - **Cardiovascular**: tachycardia, torsades de pointes and arrhythmias.
- Avoid in patients with history of **Parkinson's disease**, **convulsive disorders**, **severe cardiac disease**, **narrow angle glaucoma**, or previous **neuroleptic malignant disorder**.

Practical Tips

- For delirium or agitation in the elderly, give **very small doses of haloperidol or loxapine**, and repeat if necessary.
- Dosing of any agent is very much a balancing act of clinical effectiveness and resultant side effects. **Avoid high doses** in general to minimize adverse reactions.
- Typical antipsychotics tend to have **greater efficacy** in patients with **positive psychotic symptoms** (hallucinations and delusions) than in patients with negative psychotic symptoms.
- **Avoid abrupt cessation** in patients using high dose or long duration of use. Abrupt cessation may cause unmasking of tardive neurological side effects, cause rebound neurological side effects as well as, nausea, vomiting, tremors, sweating, tachycardia, headache and insomnia.
- Avoid using with other medications that cause **QTc prolongation**.
- Drug interactions include:
  - Metabolized by P-450 isoenzymes 3A4, 1A2 and 2D6. Thus, inducers of CYP3A4 (rifampin) may increase their clearance, while inhibitors of these enzymes (fluoxetine, paroxetine, erythromycin, ketoconazole) may decrease their clearance.
  - May potentiate the action of or have an **additive effect** on other **CNS depressants** such as **opiates, sedatives, anesthetics, or alcohol**.
  - May also antagonize the affects of levodopa.

Zopiclone

Drug Class: hypnotics, non-benzodiazepine
Drugs: **zopiclone** [Imovane, Rhovane]

Mechanism of Action & Indications

- For symptomatic relief of transient and short term **insomnia**.
- A cyclopyrrolone derivative with pharmacologic profile similar to benzodiazepines.
- Enhances the activity of the inhibitory neurotransmitter **GABA** at its receptors in the brain. Does not appear to bind to sites corresponding exactly to benzodiazepines, but sites in the vicinity.
- Decreases sleep latency, increases sleep duration and decreases the number of nocturnal awakenings.

Common Dosages

- Zopiclone 3.75-7.5mg PO 40min before retiring PRN

Adverse Effects & Contraindications

- Common side effects include **drowsiness**, **dizziness**, **confusion**, anterograde amnesia, agitation, impaired coordination, increased daytime restlessness or anxiety.
- **Metallic taste** as zopiclone is secreted in saliva.
- **Risk of dependence** is increased if there is a history of **alcoholism** or drug abuse.
- CONTRAINDICATED in patients with **severe respiratory dysfunction** such as **sleep apnea**.

Practical Tips

- Hypnotic that may have **fewer** side effects than benzodiazepines.
- Avoid prescribing late at night to prevent **daytime drowsiness**.
- As with any medication that can **alter cognition**, avoid prescribing for patients with **underlying dementia** or susceptibility for altered level of consciousness.
- Hepatically metabolized, primarily renally excreted. Thus, decrease the dose (e.g. 3.75mg) for the **elderly** and patients with **hepatic insufficiency** and **renal insufficiency**.
- Abrupt discontinuation can lead to symptoms of **withdrawal**.
- Duration of therapy should not exceed 7-10 consecutive days.
- Drug interactions include:
  - Increased **CNS depression** with: **ethanol**, **sedatives**, **antihistamines**, **anticonvulsants** and **psychotropic** medications.
  - Increased zopiclone levels with: grapefruit juice, azole antifungals, ciprofloxacin, some macrolides, verapamil, NSAIDS and other CYP3A4 and CYP2C8/9 inhibitors.
  - Decreased zopiclone levels with: carbamazepine, phenobarbital, phenytoin, rifampin and other CYP2C8/9 and CYP3A4 inducers.

"A miracle drug is a drug that will do what the label says it will do."

Eric Hodges. Episode Atheneum 63.

Written by Winnie Leung; reviewed by Peter Hamilton

ANTIEPILEPTICS

Carbamazepine

Drug Class: anticonvulsants, analgesics
Drug: **carbamazepine** [Tegretol]

Mechanism of Action & Indications

- **Sodium channel inactivation** leading to a reduced ability of neurons to fire at high frequency.
- Effective in the treatment of **simple partial**, **complex partial** and **generalized tonic clonic seizures**, but it is ineffective in the treatment of absence and myoclonic seizures.
- Other indications include **trigeminal neuralgia**, **neuropathic pain**, **bipolar disorder**, and **acute mania**.

Dosages

- Carbamazepine 100-200mg/day as initial dose is recommended.
- Available in **regular** and **extended-release** tablets. Regular carbamazepine is divided into 3-4 doses while the extended release formulation is divided into 2 doses.
- The dose can be increased gradually by **200mg** a week. Dose escalation should be titrated balancing between the side-effect profile and ongoing seizures. Average maintenance dosage ranges from **7.5-12 mg/kg/day**.

Adverse Effects

- Common side effects include **nausea**, **headache**, **dizziness**, **incoordination**, **vertigo**, **tiredness** and **diplopia**.
- The incidence of **rash** with carbamazepine varies from 2-17%.
- Infrequent **hepatotoxicity** can occur either from a hypersensitivity reaction or through a direct toxic effect of carbamazepine.
- Although carbamazepine associated **aplastic anemia** is rare, the mortality is high.
- **SIADH leading to hyponatremia** is a common side effect, especially in the elderly.

Practical Tips

- **Loading dose** can lead to **significant side effects** and it is not recommended.
- Time to steady state is approximately **2-4 weeks** for naïve patient, and **2-6 days** for patients who were recently on carbamazepine.
- Potent inducer of the **cytochrome P450 system**, therefore always be aware of potential **drug interactions**. In particular, it decreases the efficacy of **oral contraceptives** and **warfarin**.
- It is a good idea to check **complete blood count**, **electrolytes** and **liver function tests** when initiating this medication and 6-8 weeks thereafter. Routine blood monitoring every 3-6 months is NOT necessary.
- Female patients should be counseled about the **teratogenicity** of this drug.
  - **Folic acid** 2mg/day should be prescribed to all women in the childbearing age.
  - **Vitamin K** 10mg/day is recommended in the last one month of pregnancy.
- Gradually taper over at least 3 months when withdrawing drug.

Written by Martina Puchyr; reviewed by S. Nizam Ahmed and Alice Chan

Gabapentin

Drug Class: anticonvulsants, analgesics
Drugs: gabapentin [Neurontin]

Mechanism of Action & Indications

- Initially developed as a **gamma-aminobutyric acid** (GABA) **agonist**; however, the mechanism by which gabapentin exerts its anticonvulsant action and its analgesic action is unknown.
- Used in combination with other anticonvulsant agents in the management of **partial seizures** with or without secondary generalization in adults who are not satisfactorily controlled by conventional therapy.
- Used in the treatment of **neuropathic pain** associated with a variety of conditions, including postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, multiple sclerosis, HIV-related peripheral neuropathy, and cancer.

Common Dosages

- For seizure control start gabapentin 300mg once a day on day 1, 300mg BID on day 2, and 300mg TID on day 3 onward. Starting at 300mg TID is also an option. Adjust further as required. Maximum daily dose 3600 mg.
- For postherpetic neuralgia, use a similar titration schedule to maximum dose of 600mg PO TID.
- For diabetic neuralgia and others, pain relief may require considerably higher doses.
- Maximum daily dose is 3600mg/day for short durations.

Adverse Effects

- Generally well tolerated.
- Adverse CNS events include **somnolence**, **dizziness**, **ataxia**, **fatigue**, **emotional lability**, and **nystagmus**.

Practical Tips

- Antiepileptic drugs should **not** be **abruptly** discontinued.
- Clinical trials have shown that **high dose gabapentin** (2400-3600mg/day) is as effective as tricyclic antidepressants in treating **post hepertic neuralgia** and **diabetic neuropathy**. Benefit of its use in other other pain syndromes is inconclusive.
- Gabapentin is eliminated by **renal excretion** as unchanged drug. Dosing should be modified in elderly patients, and in patients with impaired renal function.
- Gabapentin does not bind to plasma proteins, is not appreciably metabolized, **does not induce hepatic enzyme activity**, and does not alter the pharmacokinetics of commonly used anticonvulsant drugs. This makes it a potentially **attractive choice** in patients where there is a need to **avoid** anticonvulsants that **impact hepatic metabolism** of other agents (i.e. enzyme induction).
- Concomitant use of **morphine** in patients receiving **gabapentin** may result in increased plasma concentrations of gabapentin, leading to a **synergistic analgesic effect**.

"Drug interactions per se are no threat to a patient; a physician's ignorance either through lack of knowledge of interaction or through lack of adequate observation of the patient and proper interpretation of new events is dangerous."

Kenneth Lloyd Melmon, Howard Fred Morreli. Clinical Pharmacology 1978; 982-1007.

Written by Nader Elmayergi; reviewed by Sanjay Kalra

Phenytoin

Drug Class: anticonvulsants, analgesics
Drug: **phenytoin** [Dilantin]

Mechanisms of Action & Indications

- Inhibits neuronal voltage-dependent **sodium currents**, which reduces the spread of seizure discharge from a focus.
- Effective in the treatment of **partial and generalized tonic-clonic seizures**. Widely used in the treatment of **status epilepticus**. Not effective in myoclonic and absence seizures.
- Also used in management of **neuropathic pain** and **myotonia**.

Dosage

- Phenytoin 5 mg/kg/day PO daily-BID in newly diagnosed adult patients with epilepsy.
- For recurrent seizures, a loading dose can be given **orally** or **intravenously**.
- For status epilepticus, a **loading dose** of 20mg/kg can be used at a rate of 50mg/minute (50mg over 2-3 minute in geriatrics and unstable cardiopulmonary condition). Cardiac monitoring is recommended. Maximum dose is 1.5g/day. Start maintenance dose 12-24 hour after loading.

Adverse Effects

- Acute toxicity is associated with **delirium**, **nystagmus**, **ataxia**, **incoordination**, **dysarthria** and **hand tremors**.
- Hypersensitivity reaction is most often associated with **skin** rash but can rarely be associated with hepatic failure, Stevens-Johnsons syndrome and toxic epidermal necrolysis.
- **Chronic** treatment with phenytoin can be associated with **cerebellar atrophy**, **peripheral neuropathy**, **gingival hyperplasia**, **hirsutism** and **metabolic bone disease**.

Practical Tips

- Since phenytoin exhibits **zero-order kinetics**, dose increments should be **gradual**, in order to avoid toxicity.
- Phenytoin can also interact with tube feeds; therefore, continuous feeds should be held 2 hours before and after the phenytoin dose.
- Therapeutic monitoring:
  - Normal value is **40-80 μmol/L**, but toxicity may occur at any concentration.
  - A low serum level does not require a dose increase if patient is seizure-free.
  - Phenytoin is highly protein bound. Thus, one should **correct serum levels** in patients with **hypoalbuminemia** or **renal failure**. Alternatively, the **free phenytoin concentration** (normally **4-8 μmol/L**) could be used for monitoring.
  - Frequency of monitoring:
    - PO: 4-7 days after initiation, then in 3-5 weeks, then every 6-12 months
    - IV: 4hr after loading dose (to assess if patient properly loaded)
    - 2-4 weeks after start/stop enzyme inducers or change in dose
- Phenytoin is a potent enzyme inducer through **cytochrome P450 system**. It can therefore reduce the efficacy of **oral contraceptives** and lead to sub-therapeutic INR levels in patients treated with **warfarin**. If a patient is on multiple medications, review drug interactions before initiating phenytoin.
- Given the potential for **teratogenicity** and **known cosmetic side effects**, avoid use of phenytoin in young female patients (where possible).
  - Prescribe **folic acid** 2mg/day in all patients in child bearing age on phenytoin.
  - Prescribe **vitamin K** 10mg/day in the last month of pregnancy to prevent hemorrhagic complications of the newborn.
- Supplement **vitamin D** and **calcium** should be given to all patients on long term treatment with phenytoin.

Written by Raj Padwal; reviewed by S. Nizam Ahmed and Alice Chan

Valproic Acid

Drug Class: anticonvulsants, antimanics, migraine prophylaxis
Drug: **valproic acid** [Epival, Depakene]

Mechanism of Action & Indications

- Mechanism has not been established, but likely multiple including an **increase** in concentrations of the **inhibitory neurotransmitter gamma-aminobutyric acid** (GABA).
- A drug of choice for **myoclonic seizures** in the syndrome of juvenile myoclonic epilepsy, **absence seizures** and for other seizures associated with **primary generalized epilepsy**. It can be used in all other seizure types.
- Used as monotherapy or as part of combination therapy with lithium, antipsychotic agents such as olanzapine, and antidepressants in the treatment of **acute manic episodes** in bipolar disorders.
- Indicated in the **prophylaxis of migraine headaches**. There is no evidence that it may be useful in the treatment of acute migraine.

Common Dosages

- For seizure control, valproic acid 10-15mg/kg PO daily initially. Increase by 5-10mg/kg/week to achieve optimal response. If the total daily dose exceeds 250 mg, it should be given in 2 or 3 divided doses. Therapeutic valproate serum concentrations for most patients with epilepsy will range from 50 to 100μg/mL.
- For manic episode, valproic acid 250mg PO TID initially. Maximum dose 60mg/kg/day.
- For migraine prophylaxis, valproic acid 250mg PO BID.

Adverse Effects & Contraindications

- Rare but serious effects include **hepatic failure**, **pancreatitis**, **coma** and **metabolic acidosis**.
- Common side effects are **gastrointestinal upset**, **sedation**, **tremor**, and **weight gain**.
- **Alopecia** is an important, although infrequent, adverse effect.
- **Thrombocytopenia** is not uncommon and is dose dependent.
- Valproic acid should not be administered to patients with hepatic disease or **significant hepatic dysfunction**.

Practical Tips

- Valproic acid may be given **intravenously** in patients already stabilized on oral valproate products. The total daily intravenous dose is equivalent to the total daily oral dose.
- Patients should be monitored especially closely in the **first 6 months** for signs of **hepatic dysfunction**. Liver function tests during this period must be done.
- Toxicities tend to occur at serum drug levels **>100μg/ml** (therapeutic range 40-100μg/ml).
- Antiepileptic drugs should **not** be **abruptly** discontinued.
- Valproic acid is highly protein bound and susceptible to protein binding interactions.
- Caution in dosing is advised in the **elderly** due to reduced elimination.
- Female patients should be counseled about the **teratogenicity** of this drug. **Folic acid** 2mg/day should be prescribed to all women in the childbearing age who are on valproic acid. Those planning a pregnancy should take folic acid 5mg/day in the preconception period and throughout pregnancy.

"Drugs don't work in patients who don't take them."

Everett Koop, US Surgeon General

Written by Nader Elmayergi; reviewed by Sanjay Kalra

ASTHMA & COPD DRUGS

Inhaled β-Agonists

Drug Class: β2-adrenergic agonists, bronchodilators
Drugs: **fenoterol** [Berotec], **formoterol** [Oxeze], **isoproterenol** [Isuprel], **salbutamol** [Ventolin], **salmeterol** [Serevent], **turbutaline** [Bricanyl]

Mechanism of Action & Indications

- Bronchial **smooth muscle relaxation** by action on β2 receptors. May also **enhance mucociliary clearance**.
- Short-acting β2-agonists (e.g. salbutamol) for treatment of **acute asthma** and/or **prevention** of exercise-induced asthma, as well as **rescue** medication in **COPD**.
- Long-acting β2-agonists (e.g. salmeterol, formoterol) for patients requiring **higher-dose inhaled corticosteroids** and/or **nocturnal asthma**, and patients with **COPD of moderate severity** (reduces dynamic hyperinflation).

Common Dosages

- Formoterol 12mcg i puff BID
- Salbutamol MDI 100mcg i-ii puffs prn or 2.5mg NEB prn (or q4h ATC if acute exacerbation)
- Salmeterol MDI 25mcg ii puffs BID or Diskus 50mcg i puff BID
- Fenoterol MDI 100mcg i-ii puffs TID-QID
- Turbutaline turbuhaler 500mcg 1-6×/day

Adverse Effects

- More commonly, **tremor** and **tachycardia**.
- In high doses, risk of **hypokalemia** and **hyperglycemia** (diabetics).

Practical Tips

- Increased risk of **death** is associated with the **chronic use of isoproterenol and fenoterol**. Short-acting agonists albuterol and turbutaline are not associated with increased risk of death.
- **Long-acting salmeterol** should **not** be used in **acute asthma** (increased mortality). However, formoterol can be used as rescue (safety margin 96 mcg/day).
- Formoterol is **full agonist** whereas salmeterol is **partial agonist**; therefore, if poor response to one, try the other.
- For exercise-induced asthma, salbutamol should be **given 15 minutes pre-exercise**.
- Formoterol has more rapid onset (**5 minutes**) of action than salmeterol (**20 minutes**).

"One person prescribes a drug, another dispenses it, somebody else takes it and somebody else pays for it."

Marc O Mayer. On lack of incentives to limit price increases of prescription drugs. NY Times 11 May 91.

Inhaled Anti-Cholinergics

Drug Class: anticholinergics, bronchodilators
Drugs: **Ipratropium** [Atrovent], **tiotropium** [Spiriva]

Mechanism of Action & Indications

- Inhibits action of acetylcholine on bronchial smooth muscle causing **bronchodilation**.
- May be considered in **asthmatics not adequately controlled** with moderate doses of inhaled corticosteroids and long-acting ß-agonist.
- Regularly scheduled dosing in **COPD**.

Common Dosages

- Ipratropium MDI 20mcg ii puffs QID or 500mcg NEB QID (or q4h ATC in acute exacerbation)
- Tiotropium 18mcg i inhaled capsule daily

Adverse Effects

- More commonly, **dry mouth** and **taste disturbance**.
- **Mydriasis** and **glaucoma** if contact with eyes.
- **Urinary retention** in the elderly.

Practical Tips

- If history of **glaucoma**, avoid using nebulized treatment with mask. Use mouth piece instead.
- If **peanut or soy allergy, avoid Combivent** (ipratropium + salbutamol) MDI as it contains a soy lecithin suspending agent. Note that the new Atrovent HFA MDI no longer contains soy lecithin suspending agent so is now safe in these patients.

"Doctors pour drugs of which they know little, to cure diseases of which they know less, into human beings of whom they know nothing"

Voltaire

Written by Marc Bibeau; reviewed by Eric Wong and Gregg Holowaychuk

Inhaled Steroids

Drug Class: inhaled corticosteroids, anti-inflammatory
Drugs: **budesonide** [Pulmicort], **fluticasone** [Flovent]

Mechanism of Action & Indications

- Increases **apoptosis** and **decreases recruitment** of airway **eosinophils**.
- The **initial maintenance** treatment for **symptomatic asthma**.
- Use in **moderate to severe COPD** if **recurrent** (>3 per year) and in **acute exacerbations**.

Common Dosages

- Budesonide Turbuhaler 200mcg ii puffs BID, or 0.5mg NEB BID
- Fluticasone 125mcg ii puffs BID, or Diskus 250mcg i BID

Adverse Effects

- More commonly, **oral candidiasis** and **dysphonia**, both of which can be reduced by use of aerochamber (with MDI only) and rinsing of mouth.
- 20-40% of administered dose is systemically absorbed, so may see **systemic steroid effects** if used in high doses and/or long-term.
- Accelerated decrease in **bone mineral density**, particularly in postmenopausal women.
- Increased prevalence of cataracts.
- Adrenal suppression when combined with inhibitors of cytochrome P450 3A4 (e.g. itraconazole and macrolide antibiotics).

"Do not rashly use every new product of which the peripatetic siren sings. Consider what surprising reactions may occur in the laboratory from the careless mixing of unknown substances."

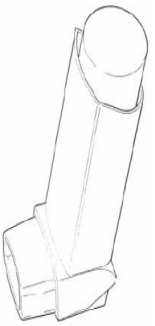
Thayer, WS. Osler the Teacher, in Olser and other papers, 3.

Written by Marc Bibeau; reviewed by Eric Wong and Gregg Holowaychuk

Inhaled Delivery Devices

How to use a metered dose inhaler

1. Remove cap and shake inhaler
2. Breathe out gently
3. Put mouthpiece in mouth and at start of inspiration, which should be slow and deep, press canister down and continue to inhale deeply
4. Hold breath for 10 seconds, or as long as possible then breathe out slowly
5. Wait for a few seconds before repeating steps 2-4



ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE METERED DOSE INHALER

© NARTC

How to use the Turbohaler

1. Unscrew and lift off white cover. Hold turbohaler upright and twist grip forwards and backwards as far as it will go. You should hear a click
2. Breathe out gently, put mouthpiece between lips and breathe in as deeply as possible. Even when a full dose is taken there may be no taste
3. Remove the turbohaler from mouth and hold breath for about 10 seconds. Replace the white cover

ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE TURBOHALER

© NARTC

Adopted with permission from the Respiratory Training Centre, Warwick
www.nrtc-usa.org

Feature	MDI without a spacer	DPI
Inspiration	• should be slow (over several seconds) • need to coordinate inspiration with medication (spray) release	• should be fast • inspiration itself "sucks" the medication into the lungs – no coordination required (breath actuated)
Sensation	• patients can feel the spray entering the mouth	• there is no sensation • patients may feel like they're not receiving any medication
Loading the medication	• no loading is required – each press of the canister releases the medication as a spray	• a capsule containing the dry powder medication needs to be loaded into the chamber (eg. by turning a knob, etc)
Types of delivery systems	• there is only one type of MDI in common use – the canister	• Turbuhaler • Diskus

Adopted with permission from the Respiratory Training Centre, Warwick
www.nrtc-usa.org

Theophylline

Drug Class: respiratory smooth muscle relaxant
Drug: **theophylline** (Apo-Theo LA, Theo-Dur, Theolair, Uniphyl)

Mechanism of Action & Indications

- Theophylline, a **xanthine** derivative, directly relaxes bronchial smooth muscle, producing **bronchodilation** and increasing flow rates and vital capacity. It also has a stimulating effect on the **CNS** (respiratory center) and **cardiac muscle,** and is associated with a mild diuresis.
- At the cellular level, theophylline leads to translocation of intracellular calcium, accumulation of cyclic AMP, and adenosine receptor blockade. It is also postulated to **stimulate mucociliary clearance**, inhibit histamine release, **suppress mediator-induced inflammation**, and **improve diaphragmatic contractility**.
- Theophylline is used in the symptomatic relief or prevention of **bronchial asthma** and reversible bronchospasm associated with **chronic bronchitis** and **emphysema**.
- Unlabelled uses include treatment of apnea and bradycardia of prematurity.

Common Dosages

- TheoDur 200-300mg BID
- Theolair 16-20mg/kg div TID-QID
- Uniphyl 400-600mg PO daily, take with evening meal

Adverse Effects

- **Central nervous system**: headache, insomnia, restlessness, tremor.
- **Gastrointestinal**: nausea, vomiting.
- **Cardiorespiratory**: tachycardia, palpitations, tachypnea.
- **Genitourinary**: transiently increased urinary frequency (mild diuresis).

Practical Tips

- Theophylline has a **narrow therapeutic index**. This makes cautious dosage determination and serum level monitoring prudent.
  - Distributed in the **extracellular space**; dosing is based on **lean body weight**.
  - The earliest levels that can be drawn should be **48 hours** after a dosage change or initiation of therapy, and **4 to 5 days** if severe CHF or liver disease.
  - Theophylline **trough levels** at steady state and are aimed at **40-75 μmol/L**.
  - Therapeutic **peak serum levels** at steady state are **40-110 μmol/L**.
  - Although levels **>110 μmol/L** are considered within the "**toxic range**", a toxic level may be any one in which signs and symptoms of toxicity are present.
  - **Signs and symptoms of toxicity**: vomiting (persistent and/or repetitive), seizures, tachyarrhythmias, anion gap metabolic acidosis, hallucinations, hypokalemia.
- Large inter-patient, intra-patient, and inter-formulation **variability** with regard to **pharmacokinetics** (absorption, distribution, metabolism/elimination). **Consult pharmacist** for therapeutic drug monitoring.
- **Long acting theophylline** should be given **with meals** as this enhances absorption.
- Approximately 85-90% **metabolized by the liver** (mainly P450 1A2), with 10-15% renal clearance. About 50% protein-bound, so may be affected by protein status.
- Drug interactions include:
  - Increased theophylline levels with macrolides, fluoroquinolones, cimetidine, fluvoxamine, allopurinol, propranolol, oral contraceptives and alcohol.
  - Decreased theophylline levels from carbamazepine, phenytoin, rifampin, phenobarbital, sulfinpyrazone, and smoking.
  - Isoniazid may increase or decrease theophylline levels.
  - Theophylline may increase lithium excretion.
  - Theophylline may enhance sensitivity and toxic potential of cardiac glycosides.
  - Theophylline may decrease phenytoin levels by increasing hepatic metabolism.

Written by Dayle Strachan; reviewed by Ron Damant and Gregg Holowaychuk

CARDIOVASCULAR DRUGS

Angiotensin Converting Enzyme Inhibitors (ACEIs)

Drugs: **benazepril** [Lotensin], **captopril** [Capoten], **cilazapril** [Inhibace], **enalapril** [Vasotec], **fosinopril** [Monopril], **lisinopril** [Prinivil, Zestril], **perindopril** [Coversyl], **quinapril** [Accupril], **ramipril** [Altace], **trandolapril** [Mavik]

Mechanism of Action & Indications

- Inhibit the **conversion of angiotensin I to angiotensin II**, as well as the **degradation of bradykinin** (a vasodilator).
- Cause vasodilatation, decreased aldosterone secretion, improved endothelial function, and reduced left ventricular mass, leading to an overall **cardioprotective** effect.
- In addition to treating **hypertension**, ACE inhibitors reduce **ventricular remodeling**, **decrease need for revascularization and hospitalization**, **improve hemodynamic function** and **CHF** symptoms, and **lower mortality** after **acute myocardial infarction** in high risk patients (HOPE, EUROPA, SAVE, ISIS-4, GISSI-3, CONSENSUS II, SOLVD and Chinese Captopril Study).
- In patients with **decreased renal function and proteinuria**, may slow the rate of disease progression by altering intra-glomerular pressure, reducing the mediators of glomerular and tubular hypertrophy, and decreasing systemic blood pressure.

Common Dosages

Indications	Dosages
HTN	Benazepril 10-40mg PO daily Captopril 12.5-50mg PO TID Cilazapril 0.5-2.5mg PO daily Enalapril 2.5-40mg PO daily Fosinopril 10-40mg PO daily Lisinopril 5-40mg PO daily Perindopril 4-16mg PO daily Quinapril 5-40mg PO daily Ramipril 2.5-20mg PO daily Tranolapril 1-4mg PO daily
CHF	Captopril start at 12.5mg PO TID, target 50mg PO TID Enalapril start at 2.5mg PO BID, target 10mg PO BID Lisinopril start at 5mg PO daily, target 30mg PO daily Ramipril start at 2.5mg PO BID, target 5mg PO BID

Adverse Effects & Contraindications

- May precipitate **hypotension** (especially after the first dose), **dry cough**, **muscle cramps**, **hyperkalemia** and **renal impairment**. Less common side effects include rash, loss of taste, leukopenia, and hypersensitivity reaction with angioedema.
- CAUTION in combined use of **ARBs**, **NSAIDs** and **potassium-sparing diuretics**, **renal impairment**, **hypotension due to volume depletion**, **severe heart failure**, **renovascular hypertension**, and **aortic stenosis or outflow obstruction**.
- Contraindications include **pregnancy (teratogenic)**, **bilateral renal artery stenosis**, **hypersensitivity**, and **acute myocardial infarction with hypotension**.

Written by Anmol Kapoor; reviewed by Glen Pearson, Brian Sonnenberg and Sheila Walter

Practical Tips

- In heart failure, always start with the **lowest dose possible** (in contrast to hypertension, in which a higher starting dose is acceptable). Optimal dosing is important when treating systolic heart failure.
- Check **serum creatinine, urea and electrolytes** when starting ACE inhibitors as well as before and after each dose adjustments. A **transient rise** in creatinine **<35%** is acceptable.
- **Do not** always **assume** that the worsening cough in heart failure patients is due to ACE inhibitors. Increasing cough could indicate **worsening heart failure**, therefore careful assessment is required.
- If patient complains of **dry cough** that is intolerable, substitute the ACE inhibitor with an **ARB**. It may take **3 weeks** for cough to disappear after discontinuation of ACE inhibitors. If the cough is not intolerable to the patient, continue with ACE inhibitor as many patients will develop **tachyphylaxis**—the cough will go away on its own.
- **Less effective in African populations**, possibly due to lower renin levels compared to general population.

"Because the newer methods of treatment are good, it does not follow that the old ones were bad: for if our honorable and worshipful ancestors had not recovered from their ailments, you and I would not be here today."

Confucius. In Brallier JM. Medical Wits and Wisdom: The Best Medical Quotations from Hippocrates to Groucho Marx 1993, p. 241.

Angiotensin Receptor Blockers (ARBs)

Drugs: **candesartan** [Atacand], **irbesartan** [Avapro], **losartan** [Cozaar], **telmisartan** [Micardis], **valsartan** [Diovan]

Mechanism of Action & Indications

- **Selective, reversible inhibitor** of **angiotensin II receptors**, with greater affinity towards AT1, versus AT2, receptors. This inhibits the **renin-angiotensin-aldosterone system** (normally causes vasoconstriction), leading to **vasodilatation**.
- Uses of ARBs include **hypertension** (all ARBs), **type 2 diabetes and nephropathy** (losartan, irbesartan), **stroke reduction in patients with left ventricular dysfunction and/or hypertension** (losartan), and **congestive heart failure** (valsartan).

Drug Dosages

Indications	Dosages
HTN	Candesartan 8-32mg PO daily Irbesartan 150-300mg PO daily Losartan 50-100mg PO daily Telmisartan 40-80mg PO daily Valsartan 80-160mg PO daily
CHF	Candesartan start at 4mg PO daily, target 32mg PO daily Losartan start at 12.5mg PO daily, target 100mg PO daily Valsartan start at 40mg PO BID, target 160mg PO BID
DM2/Stroke prevention	Losartan 50-100mg PO daily

Adverse Effects

- Common side effects include **hypotension** with or without orthostatic component, **dizziness**, **fatigue**, **hyperkalemia**, **dyspepsia** and **diarrhea**.
- Others include **upper respiratory tract infections**, **cough** (less common than ACE inhibitors), headache, chest pain, abdominal pain, dyspnea, rash, and **angioedema** (serious but uncommon, particularly when compared to ACE inhibitors).
- Contraindications include **hypersensitivity**, **bilateral renal artery stenosis**; and **pregnancy** (especially during the second and third trimeters).
- Use with caution in patients with **decreased volume status** (use a lower dose or avoid using altogether), **unilateral renal artery stenosis**, **pre-existing renal insufficiency**, **significant aortic or mitral stenosis**, and **hepatic impairment** (losartan only).

Practical Tips

- ARBs are usually started when patients are **intolerant of ACE inhibitors** (cough).
- The majority of effect occurs within **1-2 weeks**, with maximal effects in 3-6 weeks.
- Monitoring of serum **potassium** and **creatinine** levels is important.
- A **transient deterioration in renal function** is **acceptable** (rise in creatinine <35%).
- In type 2 diabetes, ARBs have been shown to **decrease progression to diabetic nephropathy** and **reduce microalbuminuria/proteinuria.**
- When used in patients with type 2 diabetes with hypertension and nephropathy, titrate up the ARB as tolerated with the main target endpoint of tight BP control (<125/75).
- In **CHF**, **ACE inhibitors** remain **first-line therapy**, but ARBs may be considered when ACE inhibitors are not well tolerated (current evidence is conflicting on this).
- Combination therapy with **ACE inhibitors** should be considered in patients at **high risk for hospitalization** of CHF (ValHeft trial).
- Drug interactions:
  - NSAIDs may decrease ARBs' efficacy and even further reduce renal function.
  - Potassium-sparing diuretics, potassium supplements, and trimethoprim (if high dose) can increase hyperkalemia risk.
  - ARBs may increase effects of amiodarone, fluoxetine and warfarin.
  - Carbamazepine, phenytoin and rifampin may decrease effects of ARBs.
  - Fluconazole may increase effects of ARBs.

Written by Roger Tsang; reviewed by Glen Pearson, Brian Sonnenberg and Sheila Walter

Preventing Hyperkalemia when Blocking the Renin-Aldosterone-Angiotensin System

Introduction

- **Hyperkalemia** is seen in 10-30% of hospitalized patients on ACE inhibitors. It is seen in 10% of outpatients on ACE inhibitors at one year.
- Low incidence of hyperkalemia in patients without risk factors.
- **Renal failure** is the most significant risk factor. The serum creatinine in trials using spironolactone ranged from 106 to 124 µmol/L.
- 1/3 of CHF patients have **chronic renal failure** and this is a poor prognostic marker in CHF.

Risk Factors for Developing Hyperkalemia

- **Chronic renal failure**, especially when GFR < 30mL/min
- **Diabetes mellitus** (hypo-reninemic hypo-aldosteronism leads to hyperkalemia)
- **Volume depletion**
- **Advanced age**
- **Potassium supplements**
- **Drugs** including potassium sparing diuretics, NSAIDs, β-blockers and heparin.

Practical Tips

- Measure **baseline creatinine** and calculate GFR.
- Use in **combination** with a **loop or thiazide diuretic**.
- When GFR is low, add or switch to a loop diuretic.
- Correct **metabolic acidosis** in CRF with oral bicarbonate. This will lower serum potassium.
- **Avoid other drugs** that will worsen hyperkalemia (see above).
- **Avoid dehydration** by doing daily weights and setting a target weight. Do **NOT** prescribe a fixed diuretic dose. Rather, adjust the dose according to the ideal body weight.
- Use **low dose** spironolactone.
- Start with **low doses of ACE inhibitors and angiotensin receptor blockers**, especially in CHF and chronic kidney diseases.
- **Check creatinine and potassium** one week after initiating therapy and after increasing the dose.
- Avoid or use with **extreme caution** when creatinine >150µmol/L or calculated GFR < 30mL/min.
- If potassium is consistently >5.5mmol/L, **STOP** using these drugs.

B.Palmer - NEJM Aug 5, 2004, 585 -591

"If many drugs are used for a disease, all are insufficient."

Bean WB. Sir William Osler: Aphorisms, 105.

Written by Peter Hamilton; reviewed by Glen Pearson, Brian Sonnenberg and Sheila Walter

Beta-Blockers

Drugs: **acebutolol** [Monitan, Sectral], **atenolol** [Tenormin], **bisoprolol** [Monocor], **carvedilol** [Coreg], **labetolol** [Trandate], **metoprolol** [Lopressor, Betaloc], **nadalol** [Corgard], **oxprenolol** [Trasicor], **pindolol** [Visken], **propranolol** [Inderal], **sotalol** [Sotacor], **timolol** [Blocadren]

Mechanism of Action & Indications

- β-receptor antagonists. **Negative chronotropic** and **negative inotropic** properties.
- Major indications include **hypertension**, **congestive heart failure**, **angina**, **post-myocardial infarction**, **atrial fibrillation**, and **migraine prophylaxis**.

Common Dosages

Indications	Dosages
HTN	Acebutolol 100-400mg BID
	Atenolol 50-100mg PO daily
	Bisoprolol 2.5-20mg PO daily
	Carvedilol 3.125-25mg PO BID
	Labetolol 100-600mg BID
	Metoprolol 12.5-200mg PO BID
	Nadalol 80-320mg PO daily
	Oxprenolol 60-320mg/day div BID-TID
	Pindolol 15-45mg/day div TID-QID
	Timolol 5-20mg PO BID
Acute MI	Atenolol 5mg IV over 5min, then 5mg IV 10min later, then 50mg PO q12h, then 100mg PO daily
	Carvedilol 25mg PO BID
	Metoprolol 5mg IV q2min x3 for acute MI, after 15min give 50mg PO q6h for 48hr, then 100mg PO BID
	Timolol 10mg PO BID
CHF	Carvedilol start at 3.125mg PO BID, target 25mg PO BID
	Bisoprolol start at 1.25mg PO daily, target 10mg PO daily
	Metoprolol XL start at 12.5mg PO daily, target 200mg PO daily

Adverse Effects & Contraindications

- Important side effects related to mechanism of action include **bradycardia** and **heart block**, negative inotropic activity, **hypotension**, **bronchospasm in patients with severe reactive airway disease**, and **acute pulmonary edema**.
- Sotalol can **prolong the QT interval** and predispose to torsades de pointes. Use of this agent should be limited to treatment of **arrhythmias** where benefits outweigh the risks. **ECG monitoring** of QT interval is imperative.
- CNS effects include **fatigue**, **depression**, nightmares, hallucinations, **impotence**.
- May exacerbate **hypoglycemic unawareness** in diabetics (non-selective agents especially). In addition, may worsen glycemic control. Clinical significance of this is not known.
- May **worsen symptoms of severe PVD** but not mild to moderate disease.
- **CONTRAINDICATED** in **heart block**, **asthma**, and significant **bradycardia**.
- COPD is not a contraindication unless there is a significant **bronchospastic component**.

Practical Tips

- **β1-selectivity**: β1-selective agents (**acebutolol**, **atenolol, bisoprolol, metoprolol**) are commonly used because they less commonly cause bronchospasm. At higher doses, β1 selectivity is lost.
- **Non-β-blocker effects**: **carvedilol** and **labetolol** have α-blocking effects and **sotalol** has class III antiarrhythmic properties (potassium channel blockade). **Labetolol** (β:α blocker 7:1) is commonly used in the treatment of hypertensive emergencies.

Written by Raj Padwal; reviewed by Glen Pearson, Brian Sonnenberg and Sheila Walter

- **Intrinsic sympathomimetic activity** (ISA): **acebutolol, oxprenol** and **pindolol** are partial agonists (ISA activity), and compared to pure antagonists, will partially stimulate the β-receptor. However, in comparison to endogenous agonists such as epinephrine and norepinephrine, the receptor is less stimulated, hence the '**relative blockade**'. The clinical significance is debatable. No evidence that pindolol decreases cardiac mortality, whereas acebutolol may be used if β-blocker needed in patients with an already slow heart rate (proven MI mortality benefit).
- **Water solubility**: the major β-selective agents can be remembered by the mnemonic PANTS – **P**indolol, **A**tenolol, **A**cebutolol, **N**adolol, **T**imolol, **S**otalol (wetting pants = water soluble). Water soluble agents tend to be renally excreted, have longer half lives, are less able to cross the blood brain barrier and are less likely to cause CNS side effects.
- **Carvedilol**, **metoprolol,** and **bisoprolol** are the only three proven β-blockers for CHF—start therapy when patient is euvolemic at low dose and titrate to target dose slowly.
- NEVER abruptly stop or reduce the dose of a β-blocker that has been given chronically, even if the patient was admitted to hospital with CHF exacerbation. This leads to a **rebound effect** (hypertension, angina, tachycardia), presumably due to the now unopposed stimulation of upregulated β-receptors (upregulation occurs during chronic β-blockade).
- Objective improvement in CHF may not be seen for **6 to 12 months**.
- **Metoprolol** is the most commonly used β-blocker in hypertension. In elderly individuals with hypertension, β-blockers are considered **second-line agents** as BP control and cardiovascular outcomes are less effective than other standard agents.
- In fact, a recent metaanalysis has shown that β-blockers as **first line treatment in hypertension** have a relative risk of **stroke** that was **16% higher** than other antihypertensives (i.e. RR=1.16). The risk for MI and death were similar among all antihypertensives. Thus, β-blockers might not be suitable as first line single agents for **uncomplicated hypertension** at all ages.
- If there is a compelling reason to use them (e.g. CHF or post-MI), they should **NOT** be avoided in diabetics because of concerns regarding hypoglycemic unawareness or hyperglycemia.
- Caution is indicated when prescribing in conjunction with other **negative chronotropic agents**, particularly **non-dihydropyridine calcium channel blockers** (verapamil, diltiazem) and in elderly patients.

"Far too large a section of the treatment of disease is to-day controlled by the big manufacturing pharmacists, who have enslaved us in a plausible pseudo-science. The remedy is obvious—give our students a first-hand acquaintance with disease and give them a thorough practical knowledge of the great drugs and we will send out independent, clear-headed, cautious practitioners who will do their own thinking and be no longer at the mercy of a meretricious literature which has sapped out independence."

Sir William Osler. The Treatment of Disease. Can Lancet 1909; 42:899-912.

Dihydropyridine Calcium Channel Blockers

Drugs: **amlodipine** [Norvasc], **felodipine** [Plendil, Renedil], **nifedipine** [Adalat XL], **nimodipine** [Nimotop]

Mechanism of Action & Indications

- Act chiefly by **vasodilatation** and reduction in peripheral vascular resistance.
- Act principally on the **L-channel**, which admits calcium ions required for muscle contraction.
- Primarily used to treat **isolated systolic hypertension**, **stable angina** (preferably if already on β-blocker) and in combination for **severe or resistant hypertension**.
- Unlike the non-dihydropyridines calcium channel blockers, amlodipine seems to be **safe in chronic heart failure** (Trial: PRAISE).

Common Dosages

- Amlodipine 5-10mg PO daily
- Felodipine 5-20mg PO daily
- Nifedipine extended release (XL) 30-60mg PO daily
- Nimodipine 60mg q4h x21 days in subarachanoid hemorrhage

Adverse Effects & Contraindications

- Dose-dependent peripheral vasodilatation leads to **pedal edema**, **dizziness**, **headache**, **eye pain**, and **facial flushing**. The peripheral edema can be reduced by combining with an ACE inhibitor or an ARB.
- **Abrupt withdrawal in angina** can result in **worsening** of symptoms.
- Chronic use can lead to **gum hyperplasia**.
- Use of **short-acting** capsules of nifedipine leads to vasodilatation and rapid reflex activation of the adrenergic system leading to **tachycardia**, **postural hypotension** causing ischemic stroke and death, especially in the elderly. Thus, **SHORT ACTING NIFEDIPINE SHOULD BE AVOIDED IN ALL CLINICAL CIRCUMSTANCES.**
- Contraindications:
  - In **aortic and carotid artery stenosis** as this could lead to critical ischemia.
  - **Immediately post MI**, **acute heart failure** and **unstable angina**.

Practical Tips

- Dihydropyridine calcium channel blockers have proven benefit in the treatment of **isolated systolic hypertension in the elderly** (SBP >160mmHg and DBP <90mmHg).
- Amlodipine (Norvasc) is a pro-drug undergoing hepatic metabolism to the active drug. This leads to **longer half-life and a slower onset** of action. It is used as a once daily preparation. As the elderly have reduced metabolism, a lower starting dose (2.5mg daily) should be used.
- In a quality-of-life study, amlodipine decreased **headaches**.
- Single agent long term use in diabetic nephropathy might increase the degree of proteinuria. Ramipril (ACE inhibitor) was shown to be more effective than amlodipine in slowing the decline in renal function in blacks (Trial: AASK). An ARB was superior to amlodipine in diabetic nephropathy (Trial: IRMA).
- **Nifedipine** is now available in a **slow release preparation** (Adalat XL). This significantly reduces side effects and makes it a once daily preparation.
- **Nimodipine** (Nimotop) is used to **prevent vasospasm** in subarachnoid hemorrhage.
- Compared to non-dihydropyridines, **less likely** to cause constipation and heart block.
- Can be used for symptom control in **Raynaud's syndrome**.
- Grapefruit inhibits hepatic metabolism, and may result in hypotension (CYP3A4).
- This class of drugs is very **expensive.** Amlodipine (Norvasc) is one of the most commonly prescribed cardiovascular drugs on the market. For the treatment of isolated systolic hypertension, thiazides are an alternative with a much lower acquisition cost. (Trials: MRC, SHEP, ALLHAT, INSIGHT and HOT-felodipine).

Written by Raj Padwal and Peter Hamilton; reviewed by Glen Pearson, Brian Sonnenberg and Sheila Walter

Non-Dihydropyridine Calcium Channel Blockers

Drugs: diltiazem [Cardizem, Tiazac], **verapamil** [Isoptin]

Mechanism of Action & Indications

- Verapamil and diltiazem bind to a different site on the calcium channel than the dihydropyridine calcium channel blockers.
- Non-dihydropyridine calcium channel blockers also act on nodal tissue **slowing the heart rate**.
- In addition, they reduce myocardial contractility and **decrease myocardial oxygen demand**, making them particularly useful for **stable angina**.
- Used in the treatment of **hypertension**, **stable angina**, **coronary spasm** (Prinz Metal angina), **supraventricular tachycardia**, **atrial fibrillation**, **diabetic nephropathy**, **migraine** and **Raynaud's syndrome**.
- Closer to β-blockers in their mechanism of action than dihydropyridine calcium channel blockers. However, unlike β-blockers, they are **CONTRAINDICATED in ventricular tachycardia** since they shorten the antegrade effective refractory period of the accessory bypass tract, and in **systolic heart failure**.

Common Dosages

- Diltiazem 120-360mg/day PO div daily-QID. Note: Cardizem CD and Tiazac are once daily preparations
- Verapamil 120-480mg/day PO div TID-QID for regular release, and daily-BID for slow release

Adverse Effects & Contraindications

- Act on the smooth muscle of the gut leading to **constipation**.
- Cause **less pedal edema** than dihydropyridine calcium blockers.
- **Impotence** is a rare complication.
- **Flushing** is an adverse effect specific to verapamil in up to 10-20% of patients.
- CONTRAINDICATIONS include **heart failure**, **ventricular tachycardia**, **bradycardia** and **heart block**.

Practical Tips (Specific for Non-Dihydropyridine Calcium Channel Blockers)

- Are more effective than dihydropyridine calcium channel blockers in reducing proteinuria when used in diabetic nephropathy with ACE inhibitors or ARB.
- **Drug interactions** are more likely with non-dihydropyridines than dihydropyridines.
  - CAUTION: When combined with β-blockers or digoxin, can lead to **bradycardia** and **heart block.**
  - Inhibition of CYP3A4 can lead to **carbamazepine, theophylline and cyclosporine toxicities**. Verapamil increases digoxin levels. When used in combination, drugs levels and side effects should be closely monitored. Grapefruit consumption should be avoided.
  - May enhance the **antiplatelet effect** of ASA.

Practical Tips (For Both Dihydropyridine & Non-Dihydropyridine Calcium Channel Blockers)

- All calcium channel blockers appear to be most effective as first line treatment of hypertension in the **elderly**, **blacks** and **low renin (-salt sensitive) hypertension**.
- All are useful as **add-on** for treating resistant and renal parenchymal hypertension.
- All calcium channel blockers have a better or similar effect in **reducing stroke** when compared to ACE inhibitors, thiazides, and β-blockers. However they are **less effective in reducing CHF or MI**.
- Unlike thiazide diuretics, calcium channel blockers do not have a negative impact on glucose metabolism, lipids and electrolytes.
- Overdose with any calcium channel blocker can be treated with **parenteral calcium**.

Written by Peter Hamilton; reviewed by Glen Pearson, Brian Sonnenberg and Sheila Walter

Digoxin

Drug Class: cardiac glycoside
Drug: **digoxin** [Lanoxin]

Mechanism of Action & Indications

- **Inhibits Na+K ATPase pump** in the basolateral cell membrane. Inhibition leads to an increase in intracellular Ca^{2+} which results in a **positive inotropic action**.
- Digoxin also exerts a **vagotonic action**, which **slows conduction through the AV node** and helps to control heart rate.
- Major indications include **CHF with diminished ejection fraction** and **atrial fibrillation**.

Common Dosages

- Digoxin 0.0625-0.375mg PO daily.
- If given in the acute setting (i.e. acute atrial fibrillation), a loading dose may be used to saturate tissue binding sites because the drug has a large volume of distribution.
  - *Example*: 0.5 mg IV then 0.25 mg IV q8h x 2 doses (i.e. 1 mg load given over 24 hours), then start daily dose of 0.125 mg. In the elderly and those with renal impairment (creatinine clearance <30mL/min), use ½ of this loading dose.

Adverse Effects & Contraindications

- **Digoxin toxicity** is the major adverse event to be aware of. Digoxin's mechanisms of action predispose towards **ventricular ectopy** and **tachyarrhythmia**, as well as blockade at the level of the AV node and **bradyarrhythmia**. Thus, both tachy- and bradyarrhythmias can occur, even simultaneously (e.g. paroxysmal atrial tachycardia with block).
- Digoxin toxicity may present with:
  - **Nausea and vomiting**
  - **Delirium**
  - **Hyperkalemia**
  - **Altered coloured vision**, **halos around objects**
  - Any type of arrhythmia, most commonly **accelerated junctional tachycardia** or **paroxysmal atrial tachycardia with block**
- CONTRAINDICATIONS include **ventricular fibrillation**, **2nd or 3rd degree heart block unless paced**, and **hypersensitivity.**

Practical Tips

- Digoxin toxicity requires a high index of suspicion. It can occur **even if the serum digoxin levels are in the normal range**, especially in the **elderly**.
- Digoxin is **renally excreted** and needs to be dose adjusted in renal failure.
- **Do not treat digoxin-induced hyperkalemia with calcium gluconate**. It may worsen ventricular arrhythmias.
- If atrial fibrillation, usually don't see effect of digoxin on heart rate until **hours later**, even if IV load given.
- **Digibind** (FAB fragments) is used to bind circulating digoxin and to inhibit its activity (does not lower digoxin levels) in cases of severe, life-threatening toxicity.
- Digoxin is a substrate of **P-glycoprotein**, which is a common membrane transporter found in various tissues, including the gut, brain, and kidney. Inhibitors of P-glycoprotein such as **verapamil and carvedilol** (two drugs commonly used with digoxin) **can increase digoxin levels**.
- Digoxin levels increase with amiodarone. Thus, **cut the digoxin dose by half if adding amiodarone**.
- Not as effective for atrial fibrillation in younger patients because they have higher sympathetic activity which overrides the vagal mechanism of action.

Written by Raj Padwal; reviewed by Glen Pearson, Brian Sonnenberg and Sheila Walter

Amiodarone

Drug Class: class III anti-arrthymic
Drug: amiodarone [pms-Amiodarone, Cordarone]

Mechanism of Action & Indications

- Long acting anti-arrhythmic that blocks primarily the **delayed rectifier K^+ channel**, and also to a certain extent the Na^+, Ca^{2+} channels and β-receptors. This prolongs action potential duration and effective refractory period in the atria, A-V node, conducting tissue and ventricular fibres, and helps in the restoration and maintenance of sinus rhythm.
- Indications include **ACLS** (pulseless VF/VT), **atrial fibrillation**, **atrial flutter, Wolff-Parkinson-White syndrome**, and **paroxysmal tachyarrhythmias** that failed agents.

Common Dosages

- For pulseless VF or VT (ACLS), 300mg IV push. If VF or VT recurs, give 150 mg IV.
- For acute control of arrhythmia, amiodarone 150mg IV bolus over 10 minutes, q10-15 minutes. Alternatively, infusion 360mg over 6 hours, then 540mg over 18 hours (maximum dose 2.2g/24 hour).
- For long term control of arrhythmia, amiodarone 400-800mg PO BID, then 300-400 mg PO BID for 1 month, then 400mg PO daily for maintenance. Amiodarone 200mg PO OD is usually a reasonable dose for atrial arrhythmias.
- When switching from intravenous to oral therapy in patients that require chronic use, follow the guidelines below. In general, patients requiring IV therapy would likely have a **more aggressive oral loading schedule**.
  - IV amiodarone for <1 week: amiodarone 800-1600mg/day PO.
  - IV amiodarone for 1-3-week: amiodarone 600-800mg/day PO.
  - IV amiodarone for >3 week: amiodarone 400mg/day PO.

Adverse Effects

- Important side effects include **hypotension, bradycardia, ventricular arrhythmias (uncommon), hypo/hyperthyroidism**, **interstitial pneumonitis, transaminitis, GI upset**, **micro-deposits in skin/cornea**, **photosensitivity**, **optic neuritis** and **peripheral neuropathy**.
- Pulmonary toxicity can present as single or multiple **lung nodules**.
- Increases skin sensitivity to sunlight. Patients should use precautions when in direct sunlight. A **blue-gray colour** may develop, especially in areas exposed to the sun. This colour may fade over **several months** after discontinuation of amiodarone.
- CONTRAINDICATIONS include **hypersensitivity** to **amiodarone/iodine**, **bradycardia**, **AV block** and **thyroid goiter**.

Practical Tips

- When initiating amiodarone, consider hospitalization for proper monitoring.
- **Intravenous therapy** should be restricted to **unstable patients** or those unresponsive to oral therapy.
- Check for **cardiac** (ECG, edema), **pulmonary** (pulmonary function tests), **hepatic** (liver function test), and **thyroid** (TSH, free T4) toxicities regularly.
- Use extra caution in patients with **heart failure**, **renal impairment**, **hypo- or hyperthyroidism**, **visual impairment**, **pregnancy** and **lactation**.
- Correct electrolyte disturbances, especially **potassium and magnesium**, **prior** to use and monitor throughout therapy.
- Amiodarone interacts with a number of **other antiarrhythmic agents** resulting in **elevated drug levels**. Thus, special caution should be given when prescribing amiodarone and another anti-arrhythmic agent, with regular ECG monitoring.

Written by Anmol Kapoor; reviewed by Raj Padwal and Margaret Ackman

- Amiodarone interferes with the metabolism of many drugs. Among the most serious interactions are **digoxin**, **phenytoin** and **warfarin**. The potentially dramatic increase in plasma levels of these drugs requires frequent dosage adjustment and monitoring over an extended period. Ensure proper follow-up arrangements.
- May enhance the **cardiotoxic effect** of **anesthetics**, and has been linked to an increased risk of **ARDS** postoperatively.
- The onset of action for amiodarone is **3 days to 3 week**s, with peak effect reached in 1 week to 5 months. Amiodarone's **half-life** is approximately **50 days**, and it may take 7 to 50 days for amiodarone to clear after discontinuation.

"Diseases caused by over-eating are cured by fasting; those caused by starvation are cured by feeding up. Diseases caused by exertion are cured by rest; those caused by indolence are cured by exertion. To put it briefly: the physician should treat disease by the principle of opposition to the cause of the disease according to its form."

Hippocrates. In Lloyd GER, Hippocratic Writings. Harmondsworth, England. 1978, p. 266.

Loop Diuretics

Drugs: ethacrynic acid [Edecrin], **furosemide** [Lasix]

Mechanism of Action & Indications

- Inhibits the Na/K/2Cl co-transporter in the **ascending limb of the Loop of Henle**.
- Relief from dyspnea occurs before onset of diuresis as it causes **venodilation** and preload reduction.
- Used to remove fluids in **volume overloaded states** such as CHF, ascites, and renal failure. May also be used to treat **hypercalcemia**, **hypernatremia** and **hyperkalemia**.

Common Dosages

- Furosemide 20-100mg PO/IV BID-TID
- Ethacrynic acid 25-50mg PO daily

Adverse Effects

- Na, K, Cl and H ions are lost in the urine and side effects include **hyponatremia**, **hypokalemia**, **hypochloremia**, **hypomagnesemia** and **metabolic alkalosis**.
- Compared to thiazides, there is less loss of Na and K relative to the volume loss.
- Like thiazides, has a metabolic effect that **increases insulin resistance** leading to diabetes, especially in the presence of hypokalemia. It also **increases uric acid levels**, precipitating gout.
- Rapid IV injection is **ototoxic** especially when combined with **aminoglycosides**.
- **Enters breast milk** and can delay closure of the **ductus**.

Practical Tips

- Intravenous furosemide is approximately **twice as effective** compared to oral furosemide. (e.g. furosemide 40mg IV BID ~ furosemide 80mg PO BID).
- Monitor potassium and creatinine regularly. Over-diuresis can precipitate pre-renal failure. **Reassess volume status regularly during active diuresis**.
- **Prescribe higher doses in renal failure** because the site of action is **intra luminal**.
- Use higher doses in **nephrotic syndrome** as protein bound furosemide is excreted in the urine.
- Prescribe furosemide BID or TID because it has a **short duration** of action (4 to 6 hours) and **compensatory Na retention** occurs when the drug wears off.
- Unlike thiazides it leads to **hypercalciuria** and can be used to treat hypercalcemia. Ensure adequate hydration before using.
- **Long term tolerance** occurs when hypertrophy of the distal tubule leads to increased distal tubular reabsorption of sodium. This can be overcome by blocking distal tubular reabsorption using a thiazide like diuretic, metolazone (Zaroxolyn).
- **CAUTION when combining with metolazone** as the combination can lead to severe hyponatremia and hypokalemia. Use metolazone sparingly based on body weight. Consider using alternate days (M, W, F).
- Loss of potency occurs if used alone or once daily. This is primarily due to activation of the renin-angiotensin system. The diuretic effect can be enhanced and sustained when used in combination with ACE inhibitors, angiotensin II antagonists or aldosterone antagonists.
- **Not as effective as thiazides in treating uncomplicated hypertension**. It does have a role when GFR falls and sodium retention contributes to the high BP. Consider switching from a thiazide when GFR <30ml/min.
- By interfering with vasodilatory prostaglandins **NSAIDS** lessen the renal response of furosemide. A **high salt diet** also reduces its diuretic effect and worsens hypokalemia. Furosemide also reduces the excretion of **salicylates** and can enhance toxicity of salicylates.
- Unlike thiazides, furosemide is safe to use with lithium.
- **Ethacrynic acid** is the **diuretic of choice** in patients with **severe sulpha allergy**.

Written by Peter Hamilton; reviewed by Alan McMahon and Sheila Walter

Potassium Sparing Diuretics

Drugs: amiloride [Midamor], **spironolactone** [Aldactone], **triamterene** [Dyrenium]

Mechanism of Action & Indications

- Spironolactone
  - **Competitive antagonist of the mineralocorticoid** (aldosterone) which acts on the distal tubule and cortical collecting tubule to promote sodium resorption.
  - Spironolactone 25 mg daily in addition to ACE inhibition in NYHA class III & IV heart failure **improved survival** and **reduced hospitalizations**. Two percent developed hyperkalemia. (Trial: RALES NEJM 341:753, 1999).
  - Used to **control ascites** in cirrhosis and **edema** in nephrotic syndrome.
  - With its anti-androgen effect, can be used in higher doses for the treatment of **primary hyperaldosteronism** (Conn's Syndrome). Also can be used to control **hirsutism** in females.
- Amiloride and Triamterene
  - **Block the effects of aldosterone by inhibiting influx of Na through ion channels** at the distal convoluted tubule. Unlike spironolactone, their action is independent of the activity of aldosterone.
  - Weak diuretics and commonly used in **combination with thiazide diuretics**.
    - For example, hydrochlorothiazide plus triamterene (Dyazide) and hydrochlorothiazide plus amiloride (Moduretic).

Common Dosages

- Amiloride 5-10mg PO daily
- Spironolactone 12.5-100mg PO daily

Adverse Effects

- **Hyperkalemia** especially at does in excess of 25 mg daily and in presence of renal failure. Twenty percent of patients on 50 mg daily will develop hyperkalemia.
- NOTE: Inappropriate use and lax monitoring of potassium can lead to **sudden death**.
- Spironolactone specifically also has anti-testosterone effect, which can lead to **gynecomastia** and **impotence**. This occurs mainly at doses in excess of 100mg daily.
- Unlike thiazide diuretics they do not aggravate insulin resistance or precipitate gout.

Practical Tips

- All potassium sparing diuretics result in loss of sodium **without major loss of potassium or magnesium**.

"While on the one hand I would encourage you with the firmest faith in a few drugs ("the friends you have and their adoption tried"), on the other hand I would urge you to cultivate a keenly skeptical attitude towards the pharmacopeia as a whole, remembering the shrewd remark of Benjamin Franklin, that "he is the best doctor who knows the worthlessness of the most medicines."

Sir William Osler. The Reserves of Life. St. Mary's Hosp Gaz 1907;13:95-8.

Written by Peter Hamilton; reviewed by Alan McMahon and Sheila Walter

Thiazide Diuretics

Drugs: **chlorthalidone**, **hydrochlorothiazide** [Apo-Hydro, Hydrodiuril], **indapamide** [Lozide], **metolazone** [Zaroxolyn]

Mechanism of Action & Indications

- Inhibit **sodium and chloride reabsorption** in the **distal convoluted tubule** (5 to 10% of filtered sodium). **Intravascular and extracellular volumes** decrease and cardiac output is reduced.
- Intravascular volume partially returns to normal over time. At the same time **peripheral resistance decreases** possibly because of an effect on sodium and calcium channels.
- Primary use is in the treatment of **hypertension** as single agent or in combination.
- Can be used for primary and secondary prevention of **calcium nephrolithiasis**.

Common Dosages

- Chlorthalidone 12.5-50mg PO daily
- Hydrochlorothiazide 12.5-25mg PO daily
- Indapamide 1.25-2.5mg PO daily

Adverse Events

- Increased distal tubular delivery of sodium results in increased excretion of potassium leading to **hyponatremia** and **hypokalemia**. May also directly increase secretion of potassium. Hypokalemia will reduce hypotensive effect and increase insulin resistance. Coexisting **hypomagnesemia** may make it difficult to correct K.
- Dose-dependent **increase** in **insulin resistance and triglycerides**. Less likely with indapamide.
- Can **increase uric acid levels** and precipitate **gout**.
- Cause **hypocalciuria** and can lead to **hypercalcemia**.
- Incidence of **impotence**, at 17 to 22% was doubled when compared to placebo.
- Rarely cause **sulphonamide-related side effects** such as pancreatitis, hepatitis, and interstitial nephritis.
- Increased mortality might occur when used in diabetics at high dose. May also increase the life-time risk of developing type 2 diabetes mellitus.

Practical Tips

- Thiazide diuretics have a flat dose response (low ceiling diuretics). This means that the **maximal natriuretic effect is seen at low dose** and it is seldom necessary to increase the dose beyond 25mg of hydrochlorothiazide.
- Use the lowest effective dose as side effects are **dose-dependent**. Doses in excess of 25mg hydrochlorothiazide should be avoided. Dose-dependent increase in electrolyte abnormalities leading to sudden death may occur, especially when not combined with potassium-sparing drugs.
- **Not effective with low GFR**. In general, avoid if GFR <30ml/min.
- As they act at different sites, **enhanced diuresis** can be achieved when used with **loop or potassium sparing diuretics**.
- **Slow onset of action** means that optimal blood pressure may take up to 12 wks to achieve. Long half life means that they are once daily drugs.
- Effective as monotherapy in hypertension about 50% of the time. Most effective in **low-renin hypertension** (commonly seen in elderly, North American black and obese).
- Effective in combination with **ACE inhibitors and ARBs** as these drugs block the counter regulatory effect of high renin secondary hyperaldosteronism.
  - Proven in multiple trials to be effective at lowering blood pressure, **decreasing mortality and morbidity** mainly by reducing **stroke** (Trials: MRC, SHEP, ALLHAT).
  - **Steroids, NSAIDs and high salt diet** may **reduce** the diuresis and hypotensive effect.
  - Decrease lithium dose by 50% when starting thiazides and monitor Li levels.

Written by Peter Hamilton; reviewed by Alan McMahon and Sheila Walter

Nitrates

Drug Class: nitrate vasodilator

Drugs: **isosorbide dinitrate** [Isordil], **isosorbide mononitrate** [Imdur, Ismo], **nitroglycerin**, **nitroprusside** [Nitropress]

Mechanism of Action & Indications

- Donates **nitric oxide** (NO) which, via second messengers, increases intracellular **cGMP** and promotes **relaxation in smooth muscle cells**.
- Effect of smooth muscle relaxation **greatest in veins**; less significant in arteries; least significant in small arterioles.
- Net effect is markedly increased **systemic/pulmonary venous capacitance**, **decreased left ventricular preload**, large artery dilatation and **afterload reduction**, and **overall reduction in myocardial oxygen demand**.
- Main Clinical Uses:
  - **Nitroglycerin patch/Isosorbide dinitrate/Isosorbide mononitrate**
    - **Anti-anginal**: improves myocardial supply-demand balance through its hemodynamic effects, reduces coronary spasm component.
    - **Congestive Heart Failure**: reduces preload and left ventricular wall strain, reduces left atrial and pulmonary vascular pressures protecting against pulmonary edema.
    - **Hypertension**: not 1st line. Weak antihypertensive effect as monotherapy.
  - **Sublingual nitroglycerin** (short acting – 15-30 minutes)
    - Immediate relief from **angina** symptoms.
    - Side effects limit use of higher doses via this route.
  - **Intravenous nitroglycerin** (continuous infusion):
    - **Anti-anginal** for unstable coronary syndromes.
    - **Acute pulmonary edema**: rapidly reduces pulmonary vascular pressures.
    - **Hypertensive emergency**: direct vasoactive effects.

Common Dosages

- Isosorbide dinitrate 10-40mg BID-TID (max dose 480mg/day)
- Isosorbide mononitrate [Imdur] 30-60mg PO daily (max dose 240mg/day)
- Isosorbide mononitrate [Ismo] 20mg PO BID (7 hours apart)
- Nitroglycerin patch 0.4-0.8mg/hr on 08:00, off 20:00. However, for patients with nocturnal angina, place patch on at 20:00 and off at 8:00
- Nitroglycerin spray 0.4mg/spray q5min x3

Adverse Effects

- **Orthostatic hypotension** (risk highest in dehydrated patients)
- Vasodilation induced **headache**
- **Reflex mediated tachycardia** with decreased diastolic coronary perfusion time
- Reflex mediated sodium/water retention with prolonged exposure.

Practical Tips

- To avoid tolerance with nitroglycerin patch, ensure **nitrate-free interval of 8-12 hours/day.**
- Nitroglycerin is primarily symptomatic relief with angina/acute coronary syndromes; **not shown to be of mortality benefit**.
- Have patients seated/lying when taking nitroglycerin sublingually to avoid injury if orthostatic hypotension develops suddenly.
- New recommendations for use of sublingual nitroglycerin in ACC/AHA STEMI guidelines—if no relief after 1 dose and waiting 5 minute, patients should contact EMS or be taken to ER.
- **Tachyphylaxis** (tolerance) may occur, rendering conventional doses ineffective.

Written by Mike McDonald; reviewed by Glen Pearson, Brian Sonnenberg and Sheila Walter

INOTROPES & VASOPRESSORS

Dobutamine

Drug Class: β1 adrenergic agonists, inotropes
Drug: **dobutamine** [Dobutrex]

Mechanism of Action & Indications

- Dobutamine predominantly has **β1 adrenergic** receptor effect that increases **inotropy** and **chronotropy** and **reduces left ventricular filling pressure** (by reducing systemic vascular resistance). Minimal α and β2 adrenergic receptor effects result in overall vasodilation. The net effect is increased cardiac output with or without a decrease in systemic vascular resistance.
- First line inotropic agent for **cardiogenic shock**. Dobutamine is increasingly being used to treat cardiac dysfunction associated with severe sepsis/septic shock.

Common Dosages

- Dobutamine 2.5-20mcg/kg/minute IV infusion. Titrate to desired response.

Adverse effects & Contraindications

- Cardiorespiratory side effects include **tachycardia**, **hypotension** in patients who are hypovolemic, **supraventricular arrhythmias** (particularly atrial fibrillation with a rapid ventricular response), **ventricular arrhythmias** (especially ventricular premature beats) and rarely, **ventricular tachycardia** and **angina**.
- CONTRAINDICATIONS include **idiopathic hypertrophic subaortic stenosis** (IHSS) and **hypersensitivity** to dobutamine.

Practical Tips

- Dobutamine is an **effective vasodilator** and so may cause **significant hypotension** if used in the setting of hypovolemia. If hypotension occurs, consider volume resuscitation.
- Unlike dopamine and other vasopressor, **local side effects are rare** as dobutamine is a vasodilator and does not cause significant skin necrosis if the intravenous cannula becomes dislodged. **Consequently, it may be safely given via a peripheral IV**.

"I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind--and all the worse for the fishes."

Holmes, Oliver Wendell. Currents and Counter-Currents in Medical Science iMedical Essays by Oliver Wendell Holmes. Birmingham, AL: Classics of Medicine Library; 1987, pp. 202-3.

Written by Sabrina Sandhu; reviewed by Noel Gibney and Catherine Sych

Dopamine

Drug Class: β1 adrenergic agonists, inotropes, vasopressors, dopaminergic agonists
Drug: **dopamine** [Intropin]

Mechanism of Action & Indications

- Dopamine is a **monoamine neurotransmitter** derived from the amino acid tyrosine and serves as a precursor to norepinephrine and epinephrine. It **activates dopaminergic receptors** directly and causes the **release of norepinephrine** from nerve endings and thereby indirectly stimulates **both adrenergic receptors**.
- Lower doses are mainly dopaminergic resulting in **renal** and **mesenteric vasodilation**. Higher doses are both **dopaminergic** and **β1-adrenergic stimulating** and result in **cardiac stimulation** and **renal vasodilation**. Larger doses stimulate α-adrenergic receptors.
- Indicated for inotropic support in conditions such as **septic** and **cardiogenic shock**.

Common Dosages

- Dopamine 1-5mcg/kg/minute IV infusion, maximum dose of 30mcg/kg/minute. Infusion may be increased by 1-4mcg/kg/minute at 10-30 minute intervals until optimal response is obtained.

Adverse Effects & Contraindications

- Cardiorespiratory side effects include **ectopic beats**, **tachycardia**, **angina**, **arrhythmias** especially atrial fibrillation with a rapid ventricular response and frequent ventricular premature beats.
- CONTRAINDICATIONS include **pheochromocytoma**, **ventricular fibrillation**, and **hypersensitivity** to sulfites.

Practical Tips

- In **very critically ill patients**, there is often a poor blood pressure response, even to high doses of dopamine. This is thought to due to depletion of norepinephrine from the vascular nerve endings. In these patients higher doses of dopamine result in **increasing tachycardia and arrhythmias with little BP improvement**. If this occurs, consideration should be given to using **norepinephrine infusion** instead.
- Hemodynamic effects of dopamine are **dose dependent** though there is a significant overlap with these stated ranges due to variations in pharmacokinetics and altered receptor density:
  - Low-dose (1-5mcg/kg/minute)—increased renal blood flow and urine output. This benefit is theoretical.
  - Intermediate-dose (5-15mcg/kg/minute)—increased heart rate, cardiac contractility, cardiac output.
  - High-dose (>15mcg/kg/minute)—α1-adrenergic effects leading to vasoconstriction with increased blood pressure and further increases in heart rate.
- Dopamine extravasation causes **severe vasoconstriction** and **skin necrosis** and consequently, while it is reasonable to use an infusion of dopamine via peripheral IV for a brief period, it is important to rapidly convert to **infusion by central line**.

"If we really want to live, we'd better start at once today. If we don't, it doesn't matter. But we'd better start to die."

W. H. Auden

Epinephrine

Drug Class: α and β adrenergic agonists, inotropes, vasopressors, antidotes
Drug: **epinephrine**, **adrenalin** [EpiPen]

Mechanism of Action & Indications

- **Stimulates β1 and β2 adrenergic receptors** resulting in relaxation of smooth muscles of the bronchial tree, cardiac stimulation, and dilation of skeletal muscle vasculature. Small doses can cause vasodilation via β2-vascular receptors and large doses may produce constriction of skeletal and vascular smooth muscle.
- First line therapy for **anaphylactic shock** and **salvage therapy for sepsis**.
- Also used in advanced cardiac life support in **asystole** and **pulseless electrical activity**.

Common Dosages

- For asystole or PEA arrest, epinephrine 1 mg IV every 3-5 minutes, or epinephrine 2-2.5mg diluted in 10mL NS or distilled water intratracheally every 3-5 minutes. Absorption is greater with distilled water, but causes more adverse effects on P_aO_2.
- For hypotension refractory to dopamine/dobutamine, epinephrine 1-10mcg/minute IV infusion, titrate to desired effect up to 0.1 mcg/kg/minute
- For hypersensitivity reaction, epinephrine 0.2-0.5mg IM/SC every 20 minutes to 4 hours (single dose maximum of 1 mg).
- For bronchospasm, epinephrine 0.1-0.5 mg IM/SC every 10-15 minutes to 4 hours or 0.1-0.25mg IV (single dose maximum of 1 mg). May also nebulize with 8-15 drops into nebulizer reservoirs, administer 1-3 inhalations 4-6 times/day.

Adverse Effects & Contraindications

- Major side effects include **tachycardia**, **flushing**, **hypertension**, **cardiac arrhythmias**, and **angina**, **decreased renal and splanchnic blood flow**, and **lactic acidosis**.
- **Severe skin necrosis** may occur following extravasation and consequently epinephrine should only be infused via a **central line** except for brief periods in an emergency situation.
- Other less serious side effects include **acute urinary retention** in patients with bladder outflow obstruction, nausea, vomiting, xerostomia, dry throat, weakness, and tremor. May precipitate exacerbation of narrow-angle glaucoma.
- Relative CONTRAINDICATIONS include **cardiac arrhythmias** and **angle-closure glaucoma**.

Practical Tips

- Monitor carefully for cardiac arrhythmias. Epinephrine will usually **temporarily improve blood pressure** but often **at the cost of cardiac ischemia** and eventual progressive decompensation.
- Except for a brief period in emergency situations, epinephrine should be infused via a **central line**. Ensure the patient is **adequately fluid resuscitated**.

Written by Sabrina Sandhu; reviewed by Noel Gibney and Catherine Sych

Norepinephrine

Drug Class: α and β adrenergic agonists, inotropes
Drug: **norepinephrine** [Levophed]

Mechanism of Action & Indications

- Norepinephrine stimulates both α**1** and β**1** adrenergic receptors, producing potent peripheral vasoconstriction as well as increased contractility and heart rate resulting in a net increase in systemic blood pressure and coronary blood flow. The vasoconstriction (α effect) is clinically greater than the inotropic and chronotropic (β**1**) effects.
- First line inotrope for sepsis.

Common Dosages

- Norepinephrine 0.5-1mcg/minute IV infusion, with the usual range 8-30 mcg/minute.

Adverse Effects & Contraindications

- Cardiovascular side effects include **bradycardia**, **arrhythmia**, and **peripheral (digital) ischemia**.
- CONTRAINDICATIONS include **hypersensitivity** to norepinephrine and bisulfites, **hypotension from hypovolemia** except as an emergency measure to maintain coronary and cerebral perfusion until volume could be replaced, and **mesenteric or peripheral vascular thrombosis** unless it is a lifesaving procedure.

Practical Tips

- Avoid using norepinephrine during **anesthesia** with cyclopropane or halothane anesthesia as there is an increased risk of **ventricular arrhythmias**.
- **Severe skin necrosis** may occur following extravasation and consequently norepinephrine should only be infused via a **central line** except for brief periods in an emergency situation.

"The human's "desire to take medicine" carries, however, a price tag. Nature's maladies are succeeded by iatrogenic hazards. Arising out of a restorative instinct, polypharmacy becomes itself an affliction."

Kroenke, Kurt. Polypharmacy: causes, consequences, and cure. Am J Med. 1985; 79:149-52.

Vasopressin

Drug Class: antidiuretic hormone analogs, posterior pituitary hormones, non-adrenergic vasopressors

Mechanism of Action & Indications

- Increases cyclic adenosine monophosphate (cAMP) which **increases water permeability** at the renal tubule resulting in **decreased urine volume** and increased osmolality via the V1 receptor. Also causes peristalsis by directly stimulating the smooth muscles in the GI tract.
- High concentrations of antidiuretic hormone cause **widespread constriction of arterioles** via the V2 receptor, which leads to increased arterial pressure. Intravenous vasopressin directly constricts mesenteric arterioles and decreases portal venous inflow, thereby reducing portal pressures.
- Indicated as **adjunct therapy for sepsis** (in combination with norepinephrine).
- Also used in advanced cardiac life support in **asystole** and **pulseless electrical activity**.
- Replacement therapy in **diabetes insipidus**.

Common Dosages

- For distributive shock, 0.01-0.04 units/minute IV infusion. Doses >0.05 units/minute may cause significant GI ischemia. Most case reports have used a maximum of 0.04 units/minute continuous infusion as a fixed dose.
- For out-of-hospital asystole, vasopressin 40 units IV ×1 dose. If spontaneous circulation not restored in 3 minutes, repeat one more dose.
- For pulseless VT/VF arrest, vasopressin 40 units IV ×1 dose, or 40 units diluted with NS to a total volume of 10ml given endotracheally.
- For diabetes insipidus, vasopressin 5-10 units IM/SC BID-QID prn to a maximum of 60 units/day, or 0.0005 unit/kg/hr IV infusion, double as needed every 30 minutes to a maximum of 0.01 unit/kg/hour. Dosage is highly variable and titrated based on serum/urine sodium, osmolality, fluid balance and urine output.
- For variceal bleed, vasopressin 0.4 unit IV bolus, then 0.4 to 1.0 unit/minute infusion. If bleeding stopped, continue at same dose for 12 hours, taper off over 24-48 hours.

Adverse effects

- Cardiorespiratory side effects include **increased blood pressure**, **arrhythmia**, **GI ischemia**, **digital ischemia**, **angina**, **myocardial infarction** and **bronchial constriction**.
- May also cause severe headache, fever, vertigo, urticaria, circumoral pallor, and uterine contraction.

Practical Tips

- Monitor carefully for **GI ischemia**. When using for blood pressure support in septic shock, vasopressin should be considered more as an endocrine replacement therapy with a narrow infusion range than as a titratable vasopressor.

"All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases."

Galen. In Strauss MB (ed). Familiar Medical Quotations. Boston: Little, Brown; 1968, p. 492b.

Written by Sabrina Sandhu; reviewed by Noel Gibney and Catherine Sych

LIPID LOWERING DRUGS

Ezetimibe

Drug Class: lipid-lowering agents
Drug: **ezetimibe** [Ezetrol]

Mechanism of action & Indications

- Selectively inhibits the **cholesterol transport mechanism at the brush border** of the small intestine, which leads to decreased absorption and delivery of cholesterol to the liver, reducing the hepatic cholesterol stores. This helps in **decreasing the total cholesterol, LDL, ApoB, and triglycerides**, and facilitates an increase in **HDL** in the blood.
- Indications include **hypercholesterolemia** (heterozygous familial and multifactorial), **homozygous familial hypercholesterolemia**, and **homozygous sitosterolemia** (Phytosterolemia) that is not appropriately controlled with statins alone.

Common Dosages

- Ezitimibe 10mg PO daily

Adverse Effects & Contraindications

- Musculoskeletal side effects including **myopathy**, **CK elevations** and **rhabdomyolysis**.
- Other side effects include headache, chest pain, diarrhea, hepatitis, pancreatitis and thrombocytopenia.
- CONTRAINDICATIONS include **hypersensitivity**, moderate to severe **liver disease** and unexplained **elevated serum transaminases**. Avoid use during **pregnancy** if patient also on statins or during lactation.

Practical Tips

- Other causes of hyperlipidemia should be ruled out prior to initiating treatment with ezetimibe.
- **No dosage adjustment** needed for renal and mild liver impairment, but should be used with caution and with regular follow-ups.
- Dosing should occur either **2 hours before** or **4 hours after** taking bile acid sequestrants.
- No clinically significant interactions were reported when ezetimibe was co-administered with most statins, except during pregnancy. When administered with a statin, **liver function tests** and **lipid profiles** should be performed at the start of treatment and according to the recommendations as per statins use (see HMG CoA Reductase Inhibitors).
- Should not be administered with **fibrates** as increased risk of hepatobiliary side effects.
- **Additional INR measurements** are recommended in patients treated with warfarin in whom ezitimibe is initiated.
- No study of ezetimibe to date has examined cardiovascular complications as outcome endpoints.

Written by Anmol Kapoor; reviewed by Dawna Gilchrist

Fibric Acid Derivatives

Drug Class: lipid-lowering agents
Drugs: **fenofibrate** [Lipidil micro/supra], **gemfibrozil** [Lopid]

Mechanism of Action & Indications

- Fibrates bind to **PPAR** (Peroxisome proliferator activated receptor-α) to modulate the expression of key genes of **lipid transport** and **metabolism** in organs such as the liver and adipose tissue. This causes **elevation of HDL**, **reduction in TG** and a **shift in the dense LDL phenotype to receptor-active, buoyant LDL** (less atherogenic).
- Also may have pleiotropic, **anti-inflammatory effects** (i.e. down regulating expression of genes encoding acute phase proteins and inflammatory cytokines).
- Agents of choice for patients with **↑↑TG and ↑LDL**, or **↑TG and ↓HDL**.

Common Dosages

- Fenofibrate 100mg PO TID with meals
- Fenofibrate micro (Lipidil Micro) 200mg PO daily with main meal, or 67mg PO BID-TID with meals
- Fenofibrate microcoated supra (Lipidil Supra) 160mg PO daily taken with main meal
- Gemfibrozil 600mg PO daily-BID 30 minutes before meals

Adverse Effects

- Common: **abdominal pain**, **diarrhea**, **muscle pain**, **rash**.
- Less common: headache, pruritus, decreased libido, dizziness, drowsiness, arthralgia, hyperglycemia, sleep/vision changes.
- Rare: **myopathy**, **increased liver enzymes**, gallstones, anemia, impotence, renal dysfunction, rhabdomyolysis.
- CONTRAINDICATIONS include **severe hepatic/renal failure**.

Practical Tips

- Type of fenofibrates:
  - **Non-micronized fenofibrate.**
  - **Micronized fenofibrate** has 50% increased bioavailability compared to non-micronized fenofibrate. Lipidil Micro 200mg daily is equivalent to non-micronized 100mg TID.
  - **Microcoated fenofibrate** has 75% increased bioavailability compared to non-micronized fenofibrate. Lipidil Supra 160mg daily is equivalent to non-micronized 100mg TID.
- For patients started on fibrates, should **monitor CBC, Cr, glucose, LFTs, CK, and fasting lipids** at baseline and every 5-6 weeks during dose escalation, then 6 months to 1 year once at target.
- Drug Interactions include:
  - **Increased toxicity/levels** with use of **statins**, cyclosporine, furosemide, MAOIs, and probencid.
  - Decreased effect with use of resins, rifampin.
  - Increases the effect of chlorpropamide, furosemide, sulfonylureas, and warfarin.

Written by Alice Chan; reviewed by Glen Pearson, Brian Sonnenberg and Cindy Polivchuk

HMG CoA Reductase Inhibitors (Statins)

Drug Class: lipid-lowering agents

Drugs: atorvastatin [Lipitor], fluvastatin [Lescol], lovastatin [Mevacor], pravastatin [Pravachol], rosuvastatin [Crestor], simvastatin [Zocor]

Mechanism of Action & Indications

- **Inhibits HMG CoA reductase**, the rate-limiting enzyme for cholesterol formation in the liver to reduce the hepatocyte cholesterol content, stimulate expression of LDL receptors, and ultimately **enhance removal of LDL from the circulation**.
- May also provide benefits via lipid-independent effects, including **restoration of endothelial function** via increased nitric oxide, promotion of **plaque stability** through modulation of macrophage activation, **immunological effects**, and **antiplatelet** and **antithrombotic** actions.
- Agents of choice for patients with **↑↑LDL alone**, **↑↑LDL and ↑TG**, or **↑LDL and ↓HDL.** Also proven for **secondary risk reduction post-myocardial infarction**.

Common Dosages

- Atorvastatin 20-80mg PO daily with evening meal
- Fluvastatin 20-80mg PO daily with evening meal
- Lovastatin 10-80mg PO qhs
- Pravastatin 10-40mg PO daily
- Rosuvastatin 5-40mg PO daily (doses of 40mg contraindicated in patients predisposed to myopathy/rhabdomyolysis and in other cases should only be used under specialist supervision)
- Simvastatin 10-40mg PO daily with evening meal

Adverse Effects & Contraindications

- Common: **abdominal pain**, **constipation**, **myalgia**, headache, rash, sleep disturbance, **elevated transaminases** (>3 x upper limit of normal, dose dependent, reversible).
- Rare: **hepatotoxicity**, **rhabdomyolysis**, peripheral neuropathy, lupus-like symptoms, and impotence.
- May have more side effects with **lipophilic agents** such as atorvastatin, lovastatin, and simvastatin. Fluvastatin, pravastatin, and rosuvastatin are hydrophilic.
- Contraindications include **active liver disease**, **high alcohol intake** and **pregnancy**.
- Rosuvastatin is CONTRAINDICATED in patients receiving concurrent phenobarbital.

Practical Tips

- Comparative lipid-lowering: atorvastatin 20mg = simvastatin 40mg = pravastatin 80mg = rosuvastatin 5-10mg.
- In general, LDL is reduced by an additional 7% with each doubling of the statin dose.
- To monitor for hepatoxicity, measure liver enzymes at baseline, then at 3 months, and repeated in 3 months if change in dose.
- For statin related myopathy, monitoring CK is of little value if asymptomatic.
  - **CK>10x upper normal limits + myopathy**: discontinue statin and other lipid-lowering drugs (e.g. . niacin, fibrate).
  - **CK>10x upper normal limits + asymptomatic**: discontinue statin, and consider re-starting at a lower dose once CK returns to normal.
  - **CK 3-10x upper normal limits + myopathy**: follow the patient's symptoms and CK levels weekly until stable clinically and biochemically. If CK increasing, consider a dose reduction or a temporary discontinuation.
  - **CK 3-10xULN + asymptomatic**: continue statins. Monitor CK until normal.
- Myopathy has also been reported in the absence of a CK rise.
- Drug Interactions:
  - CYP3A4 substrates: lovastatin, simvastatin, atorvastatin. Therefore, increased toxicity with macrolides, fibrates, grapefruit juice, itraconazole, nondihydropyridine calcium channel blockers, and cyclosporine.

Written by Alice Chan; reviewed by Glen Pearson, Brian Sonnenberg and Cindy Polivchuk

ANTIBIOTICS & VACCINES

Acyclovir

Drug Class: anti-virals
Drug: **acyclovir** [Zovirax]

Mechanism of Action & Indications

- A **nucleoside analogue** that is selectively phosphorylated by viral thymidine kinase. The phosphorylated form then **selectively inhibits viral DNA polymerase**.
- Active against **HSV-1, HSV-2**, **Varicella**, and **Herpes Zoster**.

Common Dosages

Indications	Route	Dosage
Primary oral or genital herpes	PO	400mg TID for 7-10 days
Recurrent oral or genital herpes	PO	400mg TID for 5 days
Chronic suppression of oral or genital herpes	PO	400mg BID
Mucocutaneous or esophageal herpes	PO IV	400mg every 4 hours while awake (5 times daily) for 10 days or 5mg/kg/dose every 8 hours for 10 days
Herpes encephalitis	IV	10mg/kg/dose every 8 hours for 14-21 days
Chicken pox – immunocompetent adults	PO	800mg QID for 10 days
Chicken pox – immunocompromised	IV	10mg/kg/dose infused over 1 hour every 8 hours for 7-10 days
Shingles – immunocompetent	PO	800mg every 4 hours while awake (5 times daily) for 7 days. Treatment should start within 3 days of disease onset
Shingles – immunocompromised	IV	10mg/kg/dose every 8 hours for 7 day. Treatment should start within 3 days of disease onset

Adverse Effects

- Generally is a **well tolerated** and **safe** drug.
- Rare but important side effects:
  - **Acute renal failure** due to crystallization of the drug in renal tubules, which occasionally occurs with IV therapy.
  - **Delirium**, agitation, hallucinations, myoclonus, or coma.
  - **Hemolytic uremic syndrome/thrombotic thrombocytopenia purpura** may be potentially fatal.
- Common but minor side effects: **lightheadedness**, **anorexia**, **GI upset**, mild and self-limited transaminase increase.

Practical Tips

- **Nephrotoxicity** can be **minimized** by **prior hydration** (ensuring a urine output >75ml per hour while on intravenous form). **Slow infusion** of drug over one hour also helps decrease risk of nephrotoxicity.
- Dose must be **reduced** in **renal failure**.
- **CNS toxicity** more likely in patients with **significant renal impairment** using high doses of drug.
- Increased CNS effects with **probenecid** and **zidovudine**.
- **Resistance** can rarely occur in **immunosuppressed patients on chronic therapy**.

Written by Ryan Cooper; reviewed by Lynora Saxinger and Alice Chan

Aminoglycosides

Drug Class: antibiotics

Drugs: **amikacin sulphate** [Amikin], **gentamicin sulphate** [Garamycin], **streptomycin** [mainly used in tuberculosis], **tobramycin sulphate** [Tobi – for CF patients, Tobrex]

Mechanism of action & Indications

- Inhibit bacterial protein synthesis resulting in concentration-dependent **bactericidal** effect.
- Antibacterial activity is primarily directed at **gram negative aerobic bacteria**.
- Aminoglycosides are **not** effective as **single agents** against **gram positive organisms**. They may be used in a synergistic role to treat some forms of staphylococcal and streptococcal endocarditis.
- Gram negative sensitivity includes ***E. coli, P. aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter species*** and ***Serratia marcescens***, depending on local sensitivity patterns and ideally, on the specific organism's sensitivity.

Common Dosages

- Please consult an **attending physician** or a **pharmacist** before prescribing. Aminoglycosides are not absorbed orally and must be given intravenously or intramuscularly. **Once daily dosing** is simpler, less costly, and at least **as safe and effective** as multiple daily doses for therapy although the evidence is less clear when the drug is used for synergy.

Adverse Effects & Contraindications

- Concentrated in the urine and in the proximal tubular cell, and can lead to **tubular necrosis** even when toxic serum levels are not exceeded. This results in non-oliguric renal failure, which will often recover if the drug is stopped early enough.
- Directly toxic to both components of the **eight cranial nerve** leading to **deafness**, **vertigo** and **ataxia** which **may be irreversible**. **Avoid in patients with hearing loss**.
- Have **neuromuscular blocking effect** and should be **avoided in myasthenia gravis** and used with caution when using neuromuscular blocking agents.
- Toxicity increases with **age, pre-existing renal failure, volume depletion, duration of therapy, high dose,** and **use in combination with certain nephrotoxic drugs.**
- Aminoglycosides should generally NOT be used in pregnancy because of a risk of congenital deafness, but can be given to breast feeding women because of minimal excretion in breast milk or oral absorption by the infant.

Practical Tips

- The drug cost of gentamicin is **very low** relative to most alternatives.
- As these drugs are concentrated in the urine, lower doses can be used in UTI. However they **do not penetrate the blood brain barrier** and should **not** generally be used for treatment of **meningitis** (except in neonates).
- Use with caution in ICU or sedated cases as **ototoxicity** might be missed.
- Monitor **serum drug levels and creatinine** in therapeutic (as opposed to synergistic) dosing, usually **at least twice a week**. Early renal toxicity can manifest as **hypokalemia**, **renal tubular acidosis** and a slight rise in **creatinine**. Toxicity is usually, but not always, due to problems with monitoring.
- As this class of drugs has s**erious dose-related adverse effects**, they should only be used for **serious infections where safer alternatives are not available**, particularly for long courses of treatment or in patients with increased risk of toxicity.
- Aminoglycosides have been replaced to a large degree by **third generation cephalosporins**, **quinolones**, **piperacillin** and **carbapenems** because of toxicities and the need for monitoring.
- Drugs that increase toxicity include **furosemide, ethacrynic acid, NSAIDs, ACE inhibitors, angiotensin receptor blockers, cyclosporine, vancomycin, amphotericin** and **radiocontrast**.

Written by Peter Hamilton; reviewed by Stan Houston and Alice Chan

Beta-Lactams

Drug Class: antibiotics

Drugs

- **Penicillins—amoxicillin** [Amoxil], **ampicillin**, **cloxacillin**, **penicillin**, **piperacillin** [Pipracil]
- **Cephalosporins**
  - **First generation—cephalexin** [Keflex], **cefazolin** [Ancef]
  - **Second generation—cefaclor** [Ceclor], **cefprozil** [Cefzil], **cefuroxime** [Ceftin]
  - **Third generation—cefotaxime** [Claforan], **ceftazidime** [Fortaz], **cefixime** [Suprax], **ceftriaxone** [Rocephin]
  - **Fourth generation—cefepime** [Maxipime]
- **Carbapenems—imipenem/cilastatin** [Primaxin], **meropenem** [Merrem], **ertapenem** [Invanz]
- **Monobactams**—aztreonam (special assess drug requiring Health Canada approval)

Mechanism of Action & Indications

- The basic structure of all β-lactams consists of a four membered β-lactam ring. The type and structure of the side chain defines the class and pharmacokinetics of the drug.
- β-lactams are **bactericidal**. They bind to penicillin binding proteins and **inhibit bacterial cell wall synthesis**. They may also activate **endogenous autolytic enzymes**, resulting in bacterial cell lysis.
- Various bacteria differ in their **number and type of penicillin binding proteins (PBP's).** As different β-lactams have variable affinity for different PBP's, bacteria have differing β-lactam susceptibility.
- Some bacteria produce **β-lactamases** which destroy the β-lactam ring rendering the antibiotic inactive. Some penicillins therefore are combined with a **β-lactamase inhibitor** to overcome this type of resistance. For example, **tazobactam** can be added to **piperacillin** to make Piperacillin-Tazobactam [Tazocin], and **clavulanic acid** can be added to **amoxicillin** to make **amoxicillin-clavulanate [Clavulin]**.
- The spectrum of activity of β-lactams varies widely:
  - **Penicillin** covers a **narrow spectrum** of bacteria where as the **carbapenems and some penicillins (e.g. Pip/Tazo)** have a **very broad spectrum of coverage**.
  - **Penicillins** cover most **streptococcal infections** although some **resistance** has emerged (e.g. Penicillin resistant *S. pneumoniae*).
  - **Meropenem, imipenem, piperacillin and ceftazidime** have good ***P. aeruginosa*** coverage.
  - The **third generation cephalosporins, piperacillin, imipenem and meropenem** have good **gram negative coverage**.
  - **Cloxacillin, cefazolin, Pip/Tazo, imipenem**, **meropenem** and **ertapenem** have good ***S. aureus*** coverage.
  - Some ***Enterococci*** are susceptible to **amoxicillin, piperacillin, imipenem and meropenem**.
  - Aztreonam is active essentially only against aerobic gram negative bacilli.

	1st generation cephalosporins (SS-PEK)	2nd generation cephalosporins (S-HPEK)	3rd generation cephalosporins (S-HENPPEK)
Streptococcus	✓	✓	✓
Staphylococcus	✓		
Proteus	✓	✓	✓
E. coli	✓	✓	✓
Klebsiella	✓	✓	✓
H. influenzae		✓	✓
Enterobactereciae			✓
Nesseria			✓
Pseudomonas			✓

Cephalosporins Coverage: Conceptualization Scheme (✓ = spectrum of activity)

Written by Jennie Johnstone; reviewed by Karen Doucette and Alice Chan

Common Dosages

- Penicillin G 0.5-4 million units q4-6h; 75% dose for CrCl 10-50ml/min; 20-50% dose for CrCl <10ml/min
- Cloxacillin 250-500mg PO q6h
- Ampicillin 250mg-2g IV q6h; q6-12h for CrCl 10-50ml/min; q12-24h for CrCl <10ml/min
- Amoxicillin 250-500mg PO q8h; q8-12h for CrCl 10-50ml/min; q24h for CrCl <10ml/min
- Amoxicillin/clavulanate 500mg PO q8h or 875mg PO q12h; q12h for CrCl 10-50ml/min; q24h for CrCl <10ml/min. Avoid the 875 strength for CrCl<10ml/min
- Piperacillin 3-4g IV q4-6h; q6-8h for CrCl 10-50ml/min; q8h for CrCl <10ml/min
- Piperacillin/Tazobactam 3.375g IV q6h or 4.5g IV q8h;; 2.25g q6h or 3.375g q8h for CrCl 10-50ml/min; 2.25g q8h or 3.375g q12h for CrCl <10ml/min

- First generation cephalosporins
  - Cefazolin 1-2g IV q8h; q12h for CrCl 10-50ml/min; q24-48h for CrCl <10ml/min
  - Cephalexin 250-1000mg PO q6h; q8h for CrCl 50-90ml/min; q12h for CrCl <50ml/min
- Second generation cephalosporins
  - Cefuroxime 750mg IV q8h; q12h for CrCl 10-50ml/min; q24h for CrCl <10ml/min
- Third generation cephalosporins
  - Cefotaxime 1-2g IV q8h; q8-12h for CrCl 50-90ml/min; q12-24h for CrCl 10-50ml/min; q24h for CrCl <10ml/min
  - Ceftazidime 1-2g IV q8h; q8-12h for CrCl 50-90ml/min; q12-24h for CrCl 10-50ml/min; q48h for CrCl <10ml/min
- Carbapenems
  - Imipenem 500mg IV q6h; 250-500mg q6-8h for CrCl 50-90ml/min; 250mg q6-12h for CrCl 10-50ml/min; 125-250mg q12h for CrCl <10ml/min
  - Meropenem 500mg IV q6h; q12h for CrCl 10-50ml/min; q24h for CrCl <10ml/min (1-2g IV q8h for CNS and ophthalmological infections)
  - Ertapenem 1g daily; 500mg daily for CrCl <30ml/min

Adverse Effects

- β-lactams are generally well tolerated and are considered relatively non-toxic.
- **Allergic** and **hypersensitivity** reactions are the most frequent adverse drug effect.
  - **3-10%** of the population reports an allergy to penicillin (less with PO than IV).
  - True penicillin anaphylaxis is rare (1.1% have IgE mediated allergy).
  - In those with penicillin allergy, the risk of **cross-reaction** with other β-lactams is:
    - Cephalosporins 1.5% to 10%
    - Carbapenems >10%
    - Monobactams – uncommon
- Uncommon side effects include **drug induced fever**, **serum sickness**, **interstitial nephritis**, **hepatic toxicity**, **neutropenia** and **seizures**.
- Patients with infectious mononucleosis may develop a **non-allergic maculopapular rash** after receiving amoxicillin – not a true allergy, and may give penicillin safely in the future.

Practical Tips

- In the setting of renal insufficiency, all β-lactams require dose adjustments with the **exception of cloxacillin and ceftriaxone**.
- There is **excellent penetration** of all β-lactams into most tissues.
- In the absence of inflammation, levels are NIL in the eyes, brain, cerebrospinal fluid, and prostate.

Written by Jennie Johnstone; reviewed by Karen Doucette and Alice Chan

- Penicillins and cephalosporins may be given **PO, IV, or IM** depending on the specific drug; however, overall their oral bioavailability is relatively poor and **serious infections should be treated intravenously**.
- **Carbapenems and aztreonam** are given **intravenously** only.
- **Ertapenem**, the newest carbapenem, has a more limited spectrum of activity compared to imipenem or meropenem. It does not cover Enterococcus, Pseudomonas or Acinetobacter species. However it is an excellent therapeutic choice fo**r community acquired intra-abdominal infection** or **complicated skin/soft tissue infections**.
- In those on **prolonged** β-lactam therapy, monitor **CBC and renal function** regularly.

"Medicine is the only profession that labours incressantly to destroy the reason for its existence."

James Bryce

Clindamycin

Drug Class: antibiotics
Drug: clindamycin

Mechanism of Action & Indications

- **Bacteriostatic** as it works primarily by binding to the 50S ribosomal subunit of bacteria, which inhibits with the transpeptidation reaction and chain elongation.
- Has good in vitro activity against **gram positive organisms** including, *Staphylococcus aureus*, *viridans group streptococci*, *S. pyogenes*, and *S. pneumoniae*. It also has good activity against oral and intestinal **anaerobes** including, *B. fragilis*, *C. perfingens*, *Fusobacterium spp.*, *Prevotella melaninogenicus*, and *Peptostreptococcus spp.* However resistance to clindamycin can occur in any of these organisms.
- Clindamycin has high intracellular levels in phagocytic cells, high levels in **bone**, and may have a clinically relevant antitoxin effect against toxin producing strains of ***Streptococci*** and ***Staphylococci***. However, it has poor penetration into cerebrospinal fluid.
- Common uses include **orofacial infections**, cellulitis in β-lactam intolerant patients, oral treatment of diabetic foot infections, **prevention of bacterial endocarditis** in patients unable to take amoxicillin, **acne**, **bacterial vaginosis (usually topical)**, anaerobic lung abscess, **pelvic inflammatory disease** (in conjunction with gentamicin).
- Also used as a second line treatment for ***Pneumocystis jirovecii pneumonia*** accompanied by primaquine, as well as for **falciparum malaria**, usually with quinine.

Common Dosages

- Clindamycin 150-300mg PO q6h, but can be up to 600mg PO q6h for more severe infections.
- Clindamycin 600mg IV q8h, and up to 2700mg IV daily in adults for severe infections.

Adverse Effects & Contraindications

- **Gastrointestinal**—nausea, vomiting, flatulence, anorexia, esophagitis, and diarrhea (2-20%).
  - The **nausea** can be a **limiting factor** in oral dosing. Smaller doses given q6h (relative to IV q8h dosing) helps to minimize this (e.g. 450mg q6h orally is better tolerated than 600 mg q8h).
  - Usually **mild and self-limiting diarrhea** and resolves on completion of the drug.
  - Antibiotic-associated ***C. difficile*** **diarrhea** may occur during therapy or several weeks after use of clindamycin. Pseudomembranous colitis has been reported in 0.1-10% of those taking clindamycin (the risk per dose of C. difficile colitis is probably higher for clindamycin than for other antimicrobials).
  - Relative contraindications include previous **pseudomembranous colitis**, **regional enteritis**, and **ulcerative colitis.**
- Allergic reactions with a **maculopapular rash** can occur in up to 10% of those using clindamycin. **Thrombophlebitis** can occur in IV administration; contact dermatitis may also occur in topical forms.
- Other less common adverse reactions include elevated liver transaminases, jaundice, polyarthritis, neutropenia, leucopenia, agranulocytosis, thrombocytopenia purpura, and renal dysfunction.
- Clindamycin has **neuromuscular blocking properties** and therefore should be used with caution in those already using neuromuscular blocking agents.

Written by Vikaash Kumar; reviewed by Stan Houston and Margaret Gray

Practical Tips

- The dose should be **decreased to q12h in hepatic failure**, although no specific dose adjustments are necessary in renal failure. Clindamycin is not significantly removed by dialysis.
- Caution should also be exercised in using clindamycin in conjunction with **macrolides** and **chloramphenicol** since they target the same ribosomal site.
- Clindamycin has **excellent (±90%) bioavailability** by mouth so that **most infections** can be treated by the oral route. For severe infections (e.g. necrotizing fasciitis), initial therapy should start with IV formulation as the time to peak effect is slower with the oral formulation.
- Monitoring should include **observing for changes in bowel patterns, colitis, and resolutions of symptoms**. During extended therapy, CBC, liver, and renal function should be tested periodically during prolonged therapy.
- Clindamycin has a class B risk category for use in pregnancy (no evidence of risk in humans). It is excreted in breast milk, and should be avoided in neonates since it has benzyl alcohol.

"I remembered an Irish woman who once said to me, 'You know, if only you doctors could find a cure for these wretched antibiotics, you would be doing us all a good turn, and anyway all of my family in Ireland died wither of T. B. or D.T.'s and they were a damned sight happier than us lot being kept alive with your lousy drugs.'"

John Lister. N Engl J Med. 1975; 292:467-9.

Written by Vikaash Kumar; reviewed by Stan Houston and Margaret Gray

Fluoroquinolones

Drug Class: antibiotics

Drugs: **ciprofloxacin** [Cipro], **gatifloxacin** [Tequin], **levofloxacin** [Levaquin], **moxifloxacin** [Avelox], **norfloxacin** [Noroxin], **ofloxacin** [Floxin]

Mechanism of Action & Indications

- **Bactericidal** in a concentration-dependent manner though inhibition of bacterial DNA synthesis/repair by interfering with DNA gyrase (**topoisomerase II**) and **topoisomerase IV**.
- Quinolones have excellent tissue and tissue fluid penetration so that they are suitable for infections in a wide range of organ systems.
  - **More Gram negative coverage**: ciprofloxacin (good *Pseudomonas* coverage) and norfloxacin. These are often termed "urinary quinolones" as they do not have *Streptococcus Pneumoniae* coverage.
  - **Gram negative coverage with improved gram positive coverage**: levofloxacin, moxifloxacin and gatifloxacin (often termed "respiratory quinolones"). These agents are also effective against "atypical" pneumonia agents such as *Mycoplasma*, *Chlamydia*, and *Legionella*.
  - **Anaerobic coverage**: moxifloxacin and to a lesser extent gatifloxacin (neither agent covers *C. difficile*).

Common Dosages

- Ciprofloxacin 250-750mg PO BID or 200-400mg IV q12h. For severe Pseudomonal infections dose may be increased to 400 mg IV q8h.
- Levofloxacin 500-750mg PO daily or 500-750mg IV q24h. Higher doses to be used for severe infections, or may be used for 5 day course for community acquired pneumonia.

Adverse Effects

- Rare but important side effects:
  - Arthropathy: rare **tendon rupture**.
  - Cardiotoxicity: rare **QT interval prolongation**.
  - Phototoxicity: rare with newer agents.
  - Glycemic reactions including hypoglycemia (within 3 days) and hyperglycemia (within 4-10 days) can occur in ~1% of patients on oral hypoglycemics/insulin. Gatifloxacin has recently been associated with a higher incidence of dysglycemia and should be avoided in patients at risk (e.g. diabetics, elderly).
- Common but minor side effects:
  - Skin: rash, pruritus, urticaria.
  - GI: nausea, vomiting, dyspepsia, transient and mild elevation in transaminases.
  - CNS: headache, dizziness, mild tremor, drowsiness.

Practical Tips

- Most agents are available in both intravenous and oral formulations, making conversion from IV to PO route a viable option. There is **high bioavailability** with oral administration so that the oral route is appropriate **even for serious infections**.
- These drugs are **concentration dependent**–higher doses are more effective especially when treating more severe infections. The **lower doses** (ciprofloxacin) are effective for **urinary tract infections**.
- Primarily **renally excreted**, with varying degrees of hepatic metabolism:
  - Levofloxacin, ofloxacin, gatifloxacin, ciprofloxacin, and norfloxacin are largely renally eliminated. They require dosage adjustment in renal insufficiency.
  - Moxifloxacin undergoes moderate hepatic metabolism (~55%) and generally does not require dosage adjustment in renal insufficiency.

Written by Dayle Strachan; reviewed by Stan Houston and Alice Chan

- Interactions:
  - Absorption is greatly decreased when co-administered with cations which are found in antacids (often contain aluminum, magnesium, or calcium), didanosine, sucralfate, calcium/dairy, iron preparations, zinc, elemental feeds, and multivitamins. Avoid these drugs within 2 hours of fluoroquinolone dose.
  - Drugs prolonging QT interval, especially in high-risk patients.
  - When used with **warfarin**, could lead to **supratherapeutic INR – closely monitor**!
  - **Ciprofloxacin** increases **phenytoin** and **theophylline** levels and **cyclosporine** toxicity.
  - **Gatifloxacin** increases **digoxin** levels/toxicity.
  - **NSAIDs** may increase risk of **CNS stimulation** and **seizure**.

"Among the greatest discoveries of medicine are the generally belated ones that some treatments are utterly useless."

Gordon, Richard. The Alarming History of Medicine. New York: St. Martin's Press; 1993, p. 61.

Macrolides

Drug Class: antibiotics

Drugs: **azithromycin** [Zithromax], **clarithromycin** [Biaxin], **erythromycin**

Mechanism of Action & Indications

- **Bacteriostatic** properties by irreversibly binding to the 50S ribosomal subunit in bacteria which **inhibits** the translocation step of **protein synthesis**.
- Macrolides are used as an **alternative in penicillin allergic patients** as they have a similar spectrum of activity for aerobic gram positive bacteria as Penicillin G.
- They are the **drugs of choice** in infections caused by ***Mycoplasma***, ***Legionella***, ***Chlamydia*** and ***Campylobacter*** species.
- They are **first line agents** for empiric treatment of **community acquired pneumonia** and **non-gonococcal urethritis/cervicitis**.
- They are also **first line agents** for ***Mycobacterium avium complex*** and a number of other "atypical" mycobacteria, usually in combination with other agents.
- They are **second line agents** for treatment of **otitis media**, **acute exacerbations of chronic bronchitis** and **acute sinusitis**.

Common Dosages

- Azithromycin 500mg PO x1 day, then 250mg PO daily x 1-4 days
- Clarithromycin 250-500mg PO BID x 7-14 days
- Erythromycin 250-500mg PO q6-12h

Adverse Effects

- Side effects of erythromycin include **epigastric distress** (common), **allergic reactions** and **cholestatic jaundice**.
- Much **fewer** GI effects with **clarithromycin** and **azithromycin**.
- Rarely, severe reactions can occur with all macrolides including **anaphylaxis**, **Stevens-Johnson syndrome**, **cholestatic hepatitis**, and **arrhythmias**.
- Erythromycin and clarithromycin are associated with **QT prolongation**.

Practice Tips

- Clarithromycin and azithromycin have improved **oral bioavailability** (both are stable at gastric acid pH) over erythromycin as well as **improved tolerance, and a slightly broader spectrum of activity**.
- Gram positive resistance to one macrolide usually implies resistance to others.
- Drug interactions:
  - Erythromycin and clarithromycin **inhibit the liver's metabolism of numerous drugs**, including astemizole, carbamazepine, ritonavir, digoxin, triazolam, ergots, statins, rifabutin, cisapride and theophylline.
  - Erythromycin can cause **fatal levels of digoxin, terfenadine, and theophylline** leading to **QT prolongation** and **sudden death**, especially if given with a CYP3A4 inhibitor.

Written by Curtiss Boyington; reviewed by Dennis Kunimoto and Alice Chan

Metronidazole

Drug Class: antibiotics, anti-parasitic
Drug: **metronidazole** [Flagyl]

Mechanism of Action & Indications

- **Bactericidal** as intermediate products of metabolism **interact with DNA** and **inhibit its synthesis.**
- Active against most **anaerobic** and **microaerophilic bacteria**, and certain **parasites** (*Trichomonas vaginalis*, *Giardia lamblia*, *Entamoeba histolytica*).

Common Dosages

Indication	Route	Dosage
Susceptible anaerobic infections	IV	500mg q12h
	PO	500mg BID
Bacterial vaginosis	PO	500mg BID x 7d., or 2g single dose
	Intravaginal	1 applicator/d x 5d. (avoid in 1st trimester pregnancy)
Amebiasis	IV or PO	750mg TID x 10d
Giardiasis	PO	250mg BID or TID x 5-7 d or 2 g/d x 3d
C. difficile	PO	250mg QID x 10-14d

Adverse Effects

- Generally well tolerated.
- Rare but important side effects:
  - **CNS**: seizures, encephalopathy, cerebellar dysfunction, ataxia, peripheral neuropathy.
  - **GI**: pseudomembranous colitis, pancreatitis (mild).
- Minor side effects (also very rare):
  - Metallic taste.
  - Minor gastrointestinal disturbances.
  - Urethral or vaginal burning, dark or red-brown urine.

Practical Tips

- **Reliable anti-anaerobic activity**.
- Excellent **oral bioavailability**. IV route rarely necessary (e.g. NPO, malabsorption).
- First choice for ***C. difficile***, only the **PO form of metronidazole** is effective.
- Good **CNS** and **abscess penetration**.
- **Avoid** in **pregnancy** as it crosses the placenta.

Advanced Tips

- No dose adjustments required in renal insufficiency, hemodialysis, or peritoneal dialysis.
- Dose adjustment by at least 50% suggested in patients with hepatic dysfunction.
- Resistance **rarely** develops as it requires combination of several mechanisms (plasmid or chromosomally-mediated).
- **Drug interactions**:
  - Disulfiram reaction with **alcohol** (nausea, vomiting).
  - Potentiation of effects of **warfarin.**

Written by Wendy Sligl; reviewed by Geoff Taylor and Alice Chan

Trimethoprim Sulfamethoxazole (TMP/SMX)

Drug Class: antibiotic, sulfonamide derivative

Drugs: trimethoprim sulfamethoxazole [Septra, Septra DS, Bactrim, Bactrim DS]

Mechanism of Action & Indications

- Sulfamethoxazole interferes with **bacterial folic acid synthesis and growth** via inhibition of dihydrofolic acid formation from para-aminobenzoic acid.
- Trimethoprim inhibits **dihydrofolic acid reduction to tetrahydrofolate** resulting in sequential inhibition of enzymes of the folic acid pathway.
- Although trimethoprim and sulfamethoxazole exert a bacteriostatic effect when used alone, they have a synergistic **bactericidal** effect when used together.
- First line treatment for most cases of **uncomplicated urinary tract infections**. Also used for **acute otitis media**, **acute exacerbations of chronic bronchitis** (AECB), **infectious gastroenteritis**, and infections caused by **Nocardia** species**.**
- Used for prophylaxis and treatment of ***Pneumocystis jirovecI pneumonia*** **(PJP)** in immunosuppressed patients, including HIV, transplant and oncology patients.

Common Dosages

Indications	Route	Dosage
Urinary tract infections (cystitis, pyelonephritis)	PO	1 DS tab BID x 7-14 days
Acute exacerbations of chronic bronchitis	PO	1 DS tab BID x 10-14 days
Traveler's diarrhea/Shigellosis	PO	1 DS tab BID x 5 days
PJP prophylaxis	PO	1 SS tab QD
PJP treatment	PO/IV	15-20 mg TMP/kg/day in 3-4 divided doses X 21 days (+ steroids if PaO_2 < 70 mmHg)
Nocardia sp.	PO	2 DS tabs BID x months (infectious diseases consultation recommended)

- Renal impairment dosing:
  - CrCl 15-30ml/min—give 50% of recommended dose.
  - CrCl <15 ml/min—TMP/SMX not recommended.

Adverse Effects & Contraindications

- Common adverse effects include **gastrointestinal upset** (nausea, vomiting, anorexia) and **dermatologic reactions** (rash, urticaria).
- Rare but potentially life-threatening side effects include **severe dermatologic reactions** (e.g. SJS, TEN), **hepatotoxic reactions**, and pancytopenia/agranulocytosis.
- CONTRAINDICATED in patients with **history of hypersensitivity to any sulfa drug** or to **trimethoprim**, **porphyria**, **folate deficiency**, **liver failure**, **severe renal impairment**, **pregnancy at term** (risk of **kernicterus** to newborns) and infants <2 months of age.

Practical Tips

- Dosing of TMP/SMX is always in a 1:5 ratio. See table for formulations supplied:

Supplied	TMP (mg)	SMX (mg)
1 SS tab	80	400
1 DS tab	160	800
5 ml oral suspension	40	200
5 ml ampule IV solution	80	400

Note: the oral suspension has a DIFFERENT strength than the intravenous solution.

- TMP/SMX is available in generic formulation; hence it is much cheaper than other antibiotics that may be used in the treatment of UTI's or AECB's.
- TMP/SMX remains a useful first line agent for most cases of uncomplicated, community acquired urinary tract infections (cystitis, pyelonephritis, and prostatitis).

Written by Duncan Webster; edited by Isabelle Chiu and Alice Chan

Vancomycin

Drug Class: antibiotics
Drug: **vancomycin** [Vancocin]

Mechanism of Action & Indications

- Vancomycin is a complex glycopeptide, and exerts its **bactericidal** effect by **binding to peptidoglycan**, a major structural polymer of the bacterial cell wall. Its interaction with peptidoglycan is **different** from penicillin. Thus there is no cross resistance between penicillin and vancomycin.
- Because vancomycin is so large, it is unable to cross the outer cell membrane of gram negative organisms. Thus vancomycin is **ineffective for the treatment of gram negative infections**.
- Antibiotic used in the treatment of **aerobic** and **anaerobic gram positive organisms.**
- Antibiotic of choice for **coagulase negative staphylococcal infections**, **methicillin resistant *S. aureus* infections (MRSA)**, *S. aureus* infections in those patients unable to tolerate penicillins and cephalosporins, and *C. difficile* diarrhea not responding to ORAL metronidazole.

Common Dosages

- Vancomycin 1g IV q12 h or 15mg/kg IV q12h

Adverse Effects

- Early preparations in 1950's quite nephrotoxic; however, with current preparations **nephrotoxicity exceedingly rare** and not usually seen except when **co-administered** with an **aminoglycoside** (e.g. gentamicin).
- An **erythematous rash** on the face, neck and upper torso can erupt during an infusion of vancomycin sometimes referred to as **red man syndrome**. This is secondary to a non-immune release of histamine, and not an allergic reaction. It can be treated by slowing the infusion of vancomycin and giving anti-histamines.
- **Chemical thrombophlebitis** can be seen when administered via peripheral intravenous catheters.
- Drug reactions and neutropenia are rare.

Practical Tips

- Because of the availability of **other effective treatments** and **resistance** concerns, do **NOT** routinely use as first line agent in *S. aureus* infections or *C. difficile* diarrhea.
- Vancomycin is almost exclusively administered as an **intravenous form** as it is **very poorly absorbed** from the GI tract. The **exception** is in **colonic C. difficile infections** where vancomycin is given orally as the necessary drug effect is within the GI tract.
- The drug penetrates serous membranes well. It can **permeate the blood brain barrier if the meninges is inflamed**, but not under normal circumstances.
- Vancomycin is excreted via the **kidneys**. Its half-life with normal renal function is **6 hours** but extends to **7.5 days if a patient is anuric**. Thus it is important to dose adjust according to renal function. For creatinine clearance of 10-50ml/min, vancomycin should be given at 1g IV q24-96 hour, for creatinine clearance of <10ml/min or on dialysis, give at 1g IV q4-7d.
- Do serum levels if the patient has **changing renal function, chronic renal failure, or is on dialysis**. **Desired trough (pre-dose) levels** are 15-20mg/L for CNS infections, endocarditis, osteomyelitis or pneumonia, and 5-15mg/L for other indications.

Written by Jennie Johnstone; reviewed by Lynora Saxinger and Alice Chan

Vaccines for Adults

Drug Class: Vaccine

Drugs: Please refer to http://www.immunizationinfo.org/vaccineInfo/index.cfm for the trade names of each vaccine.

Mechanism of Action

- **Live vaccines** contain live organisms that multiply logarithmically in the recipient until checked by the onset of immune response it is intended to induce. They generally confer **lifelong protection** with one dose on those who respond.
- **Inactivated vaccines** contain killed organisms, providing the antigen substrate aimed at inducing immunity. The immune response is not permanent with one dose, making repeated vaccination and **booster necessary** to develop and maintain high levels of antibody. Exceptions are hepatitis B vaccine with proven ≥ 10 years immunity post-vaccination and inactivated polio vaccine, for which duration of immunity is unknown.
- **Polysaccharide vaccines** tend to induce **T-cell independent immune responses** that do not produce booster responses on repeated injections (?tolerance via anti-vaccine antibody production) and have poor immunogenicity in infants and young children.
- **Protein antigen vaccines** tend to generate **T-cell dependent immune response** with induction of immunologic memory, booster effects on repeated administration and good immunogenicity in infants and young children.
- **Covalent linkage of a polysaccharide antigen to a carrier protein** converts it from a T-cell independent to a **T-cell dependent antigen**. An example is *H. Influenzae* type B capsular polysaccharide vaccine.

Who should be asked about adult immunization?

- Patients who haven't checked their immunization for years.
- Patients whose occupation or lifestyle exposes them to infections.
- Patients who are a health care provider or caregiver.
- Patients with any chronic medical condition.
- Patients who are students living in residence.
- Patients who are a parent or grandparent.
- Patients who are gardeners or work with soil.
- Patients who plan to travel to another country.
- Patients who are pregnant or plan to be.

Common schedules

- The indications, schedules, and complications of common vaccinations are listed in the two tables to follow. Please refer to the following websites for details:
  - Children
    - http://www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1_e.html (Public Health Agency of Canada)
  - Adults
    - http://www.phac-aspc.gc.ca/im/is-cv/index.html#b (Public Health Agency of Canada)
    - http://www.phac-aspc.gc.ca/publicat/cig-gci/index.html
    - http://www.cdc.gov/node.do/id/0900f3ec8000e2f3 (Centre for Disease Control)

Written by Mao-Cheng Lee; reviewed by Stan Houston and Margaret Gray

ROUTINE IMMUNIZATION OF ADULTS			
Vaccine or Toxoid	**Indications**	**Further doses**	**Common Side Effects**
Diphtheria (inactivated organism)	All adults or adults at 50 year old requiring vaccination review or close contacts of a pertussis case	Q10 years, preferably given with tetanus toxoid (Td)	Local reactions. Febrile reactions. (increases with age)
Tetanus (inactivated toxin, aka toxoid)	All adults	Q10 years, (if patient has had a primary series of 3 doses) preferably given as Td	Rare. Local reactions. (lymphadenopathy, urticaria, anaphylaxis, serum sickness very rare)
Influenza (inactivated virus)	Adults > 65 years old High risk adults < 65 years old[1] and other select groups Health care workers. Can be used electively by healthy individuals.	Every year using current vaccine formulation	Local soreness. Fever, malaise, myalgia. GBS (1/million). Allergy (to egg component). Rarely systemic vasculitis.
Pneumococcal (polysaccharide) Use of conjugate vaccine currently limited to children but this may evolve	Adults > 65 years old; conditions with increased risk of pneumococcal diseases[2]. Pre-splenectomy Limited efficacy	Repeat x 1 at 5-6 years in high risk individuals	Mild local reactions. Low grade fever. Rare severe reactions of the Arthus. (Esp. true if revaccinated within 2 years of previous)
Mumps (live attenuated)	All adults born in 1970 or later with no history of mumps.	May be given as MMR	Malaise and fever with or without rash at 7-12 days post, and lasting upto 3 days. 1/3000- febrile convulsion. Parotitis and mild skin rashes. Rare viral meningitis without sequelae.
Rubella (live attenuated)	Susceptible women (negative serology) of childbearing age and health care workers.	Maybe given as MMR	Rash and lymphadenopathy occasionally. Common in adults: arthritis or arthralgia at 1-3 weeks post vaccine, and lasting for 1-3 weeks (esp. post-pubertal women) without recurrence.

[1] Adults and children with chronic cardiac or pulmonary disorders (i.e. asthma, CF, bronchopulmonary dysplasia) requiring regular medical followup, residents of nursing home/chronic care facilities, immunosuppressed states, health care workers.

[2] Consider re-immunization in **functional or anatomic asplenia** (give 10-14 days prior to splenectomy), **sickle cell disease**, **hepatic cirrhosis**, **chronic renal insufficiency**, **nephrotic syndrome**, **HIV** (early on, prior to ARVs), and **immunosuppressed states** (diabetes, metabolic disorders, cancer (hematologic: lymphoma, Hodgkin's, multiple myeloma), immunodeficiency disorders, immunosuppressive therapy, renal disease, anemia, hemoglobinopathy, alcoholism). Either polysaccharide or conjugate forms can be utilized.

SELECTED IMMUNIZATION FOR ADULTS	
Vaccine	**Indication**
Hemophilus B conjugate vaccine	Recommended pre-splenectomy
Hepatitis A (inactivated)	Exposure to conditions of poor hygiene, especially travel to low income countries, anal sexual contact, individuals with underlying liver disease, e.g. hepatitis C,
Hepatitis B (recombinant antigen)	Universally recommended in Canada, especially for health care workers, injection drug users, those with multiple sexual partners, work with low income country children
Combined Hepatitis A & B vaccine	As above
Meningococcal (polysaccharide A C Y W135 or protein-polysaccharide conjugate C only form, polyvalent conjugate vaccine available soon)	High risk exposure (i.e.college) or travel. Recommended pre-splenectomy.
Pertussis[1] (Only acellular purified antigen form in Canada)	No further dose recommended currently beyond that of regular children vaccination schedule. Give to only those who may not have had adequate vaccination in childhood. Adult vaccination may be recommended in future in order to reduce transmission in the community.
Poliomyelitis (inactivated IPV only)	Travel to endemic area
Varicella (live attenuated Oka strain)	Occupational (e.g. health care worker), household contact of susceptible individuals and those susceptible because of underlying disease.

[1] Whole cell pertussis vaccine not recommended for individual >7 years old. This form is no longer available in Canada.

Contraindications

- All vaccines—anaphylaxis to one or more vaccine components, severe illness.
- Live vaccines—pregnancy, generally immunocompromised (steroids, AIDS not HIV), malignancies.

"The excellence of the art of medicine does not depend on elegant prescriptions but on observation."

Thomas Sydenham

DIARRHEA & CONSTIPATION DRUGS

Stool Softeners

Drugs: **docusate sodium** [Colace], **docusate calcium** [Surfak]

Mechanism of Action & Indications

- An **anionic surfactant** that lowers stool surface tension and allow aqueous and fatty substances to mix, thereby making **stool softer**.
- Stimulates **intestinal fluid and electrolyte secretion** and alters the permeability of intestinal mucosa.
- Used as initial therapy for **constipation**, but has little effect on treating severe constipation alone.
- Also used to prevent **post-surgical straining**.

Common Dosages

- Docusate sodium 100mg PO BID
- Docusate calcium 240mg PO BID

Adverse Effects & Contraindications

- Adverse effects rare.
- Occasionally **rash**, **cramping**, **nausea**, **diarrhea**, **throat irritation** or **bitter taste** may occur.

Practical Tips

- Do NOT use with **oral mineral oil** (as leads to greater absorption of mineral oil).
- Onset of action occurs within **1-3 days**.

"It is so much easier to do a penny-in-the-slot sort of practice, in which each symptom is at once met by its appropriate drug than to make a careful examination and really to study the case systematically."

Sir William Osler. The Importance of Post-Graduate Study. Lancet 1900;2:73-5.

Anthraquinone Laxatives

Drugs: senna [Senokot]

Mechanism of Action & Indications

- Converted by bacteria into a **bowel irritant** which has direct action on intestinal mucosa including increasing the rate of **colonic motility**, enhancing **colonic transit**, **inhibiting water and electrolyte secretion**.
- Initial treatment for **constipation** or **evacuation** of colon for examinations.

Common Dosages

- Senna 2 tabs (8.6mg/tab) PO qhs

Adverse Effects & Contradictions

- Adverse effects include **fluid and electrolyte shifts** (metabolic acidosis, metabolic alkalosis, hypokalemia, hypocalcemia), **abdominal pain** (including griping, nausea or diarrhea), and **urine discoloration** (pink/red to brown/black).
- Melanotic pigmentation of the colon (i.e. **melanosis coli**) is seen in people who have used senna for 4-9 months. The condition is usually benign and reversible with discontinuation of the drug.
- Standardized senna fruit extract may contain large amounts of **sugar**, a consideration in patients with diabetes mellitus.
- CONTRAINDICATIONS include **acute surgical abdomen**, **bowel obstruction**, **fecal impaction**, and **undiagnosed abdominal pain**.

Practical Tips

- Senna requires activation in the colon; therefore, its onset of action is **6-12 hours** after ingestion.
- Senna is usually given as a single dose at **bedtime**.

"If you look over a list of medicinal recipes in vogue in the last century, how foolish and useless they are seen to be! And yet we use equally absurd ones with faith today."

Thoreau HD. Journal entry for February 18, 1860. Reprinted in The Thoughts of Thoreau. Selected by Teale EW. New York; Dodd, Mead; 1962, p. 169.

Written by Marilyn Zeman; reviewed by Winnie Wong and Melissa Dutchak

Stimulant Laxatives

Drugs: bisacodyl [Dulcolax], castor oil

Mechanism of Action & Indications

- Causes strong and widespread **peristaltic movements** of the colon. Bisacodyl works via local axon and segmental reflexes, therefore it is effective in **ganglionic blockade or spinal cord damage**.
- Bisacodyl is indicated for **evacuation** of the colon for examination, **post-surgical and spinal cord injury bowel care**, and occasionally for the treatment of **constipation** not responding to other laxatives.

Common Dosages

- Bisacodyl 5-15mg PO daily prn or 10mg PR daily prn
- Castor oil 15-60 mg PO prn

Adverse Effects & Contraindications

- Adverse effects may include **abdominal cramping**, **nausea**, **vomiting**, **fainting**, **fluid** or **electrolyte imbalances**.
- **Rectal burning** may occur with suppository use.
- CONTRAINDICATED in individuals with an **acute surgical abdomen**, **appendicitis**, **rectal bleeding**, **gastroenteritis**, or **intestinal obstruction**.

Practical Tips

- All other laxative agents are preferred over castor oil due to its unpleasant nature.
- Long term use (>7 days) is not recommended for fearing of possible **bowel dependence**.
- Oral bisacodyl has an onset of action of **6 to 12 hours** after dose, rectal bisacodyl has an onset of action of **15 to 60 minutes** after dose, castor oil has an onset of action of **2 to 6 hours** after dose, given on an empty stomach.
- Avoid milk product ingestion around bisacodyl dose.

"Expensive medicines are always good: if not for the patient, at least for the druggist."

Anonymous. Russian Proverbs. Mount Vernon, NY: Peter Pauper Press; 1960.

Written by Marilyn Zeman; reviewed by Winnie Wong and Melissa Dutchak

Osmotic Laxatives

Drugs: glycerin, lactulose, sorbitol

Mechanism of Action & Indications

- **Non-absorbable sugar** that is hydrolyzed in the intestine into an organic acid. The acidification of the luminal contents **osmotically** draws water into the lumen, which then **stimulates colonic motility**.
- Efficacious in the treatment of **opioid induced constipation**, constipation in the elderly and idiopathic chronic constipation.
- Lactulose is also used in the treatment of **hepatic encephalopathy**. The luminal acidification induced by lactulose essentially traps the ammonium ion produced by the bacterial metabolism of fecal urea by converting it into a polar ion.

Common Dosages

- Lactulose 15-30ml PO daily-BID
- Sorbitol 70% solution 30-150ml PO prn

Adverse Effects

- **Abdominal discomfort**, **distention** and **flatulence** are common in the first few days of treatment (but usually resolve with continued administration).
- Many dislike the sweet taste.

Practical Tips

- Avoid using lactulose in patients with **significant edema or heart failure** as the sodium component promotes fluid retention. Consider sorbitol instead.
- Effects may not be seen for **24-48 hours** after dosing has begun.

"The blind faith which some men have in medicines illustrates too often the greatest of all human capacities—the capacity for self-deception."

Sir William Osler. The Treatment of Disease. Can Lancet 1909; 42:899-912.

Written by Marilyn Zeman; reviewed by Winnie Wong and Melissa Dutchak

Saline Laxatives

Drugs: **magnesium citrate** [Citro-Mag], **magnesium hydroxide** [Milk of Magnesia], **magnesium sulphate** [Epsom Salts], **sodium phosphate** [Oral Fleet, Fleet Enema]

Mechanism of Action & Indications

- Poorly absorbed magnesium and phosphate ions induce catharsis by **osmotically** mediating water retention. This indirectly stimulates **GI stretch receptors** and results in **peristalsis**.
- Magnesium containing laxatives are thought to stimulate **cholecystokinin release** which promotes fluid and electrolyte secretion into the gut and possibly **increased intestinal motility**.
- Saline laxatives really represent a stronger form of osmotic laxatives.
- Indicated for **acute evacuation** of the bowel. Infrequent treatment of **constipation.**

Common Dosages

- Sodium phosphate (Fleet enema) PR x1
- Sodium phosphate (Oral Fleet) 45ml (1 bottle) PO x1

Adverse Effects & Contraindications

- Adverse effects include **dehydration** (dizziness, fainting, palpitations), as well as fluid and **electrolyte abnormalities** (hypermagnesemia, hyperphosphatemia, hyperkalemia, hypernatremia, and hypocalcemia).
- Caution in patients with **renal or cardiac disease**, pre-existing **electrolyte abnormalities** and patients on **diuretics**.
- CONTRAINDICATIONS include abdominal pain, nausea, vomiting, rectal bleeding

Practical Tips

- Limit use to **less than 1 dose per 24 hour** period as **potential of prolonging the QT interval**.
- **Orally** administered saline laxatives act mainly on the **small intestine**, while **suppositories or enemas** generally **promote colonic evacuation** only.
- Magnesium hydroxide has been found to **decrease the rate and extent** of chlordiazepoxide, chlorpromazine, dicoumarol, digoxin, and isoniazid **absorption**.
- Phosphate containing enemas can alter the **appearance of rectal mucosa**.
- Action occurs within **30 minutes to 6 hours** of oral dose, and within 15 minutes for rectal dose.

"Good judgement comes from experience, and often experiece comes from bad judgement."

Rita Mae Brown

Polyethylene Glycol Electrolyte Solution

Drug: polyethylene glycol [GoLytely]

Mechanism of Action & Indications

- Long-chain polyethelene glycol is **poorly absorbed from the gastrointestinal tract** and retains water through osmosis.
- There is **no transfer of ions across the intestinal wall** because they are made of an isotonic mixture of sodium sulfate, sodium bicarbonate, sodium chloride and potassium chloride.
- Indicated in bowel preparation for **colonoscopy** and **severe constipation**.

Common Dosages

- Polyethylene glycol 4L PO/NG x1 dose. Usually given after patient fasts for at least 2 hours (4 hours is preferable). For oral dosing, patient drinks 250ml every 10 minutes until diarrhea fluid is clear.

Adverse Effects & Contraindications

- Side effects include nausea and vomiting, abdominal bloating and cramps, flatulence, eczema, and urticaria.
- Fluid and electrolyte changes and cardiac dysrhythmia are possible.
- CONTRAINDICATED in bowel obstruction/perforation, toxic colitis, and megacolon.

Practical Tips

- Drinking **4 litres of this unpalatable fluid** can be a very **daunting** task for patients, particularly for **frail eldery**.
- Can usually be **safely** used in patient with **renal failure** or **congestive heart failure**.
- Rapid drinking of each portion is preferred to drinking small amounts continuously.
- Chilled solution often more palatable.

"Nature is merciful and does not try her children, beyond their compass. It is only when the cruelty of man intervenes that hellish torments appear."

Winston S Churchill. Recalled on Churchill's death 24 Jan 65.

Written by Marilyn Zeman; reviewed by Winnie Wong and Melissa Dutchak

Loperamide

Drug Class: piperidine butyramide derivative anti-diarrheal agents
Drug: **loperamide** [Imodium]

Mechanism of Action & Indications

- Direct effect on **cholinergic** and **noncholinergic nerve endings** and **intramural ganglia** of the intestinal wall; interferes with the **peristaltic reflex** by decreasing the activity of the longitudinal and circular muscles in the intestinal wall.
- Results in **prolonged transit time**, increased viscosity, increased bulk density, reduced daily fecal volume and diminished loss of fluid and electrolytes.
- First line anti-diarrheal agent in **chronic diarrhea**, including diarrhea associated with inflammatory bowel disease, bowel resection, organic lesions, or chemotherapy.
- Effective for **travelers diarrhea**, used alone or with antimicrobial agents.
- **Increases anal sphincter tone** so may be used to treat **anal leakage**.

Common Dosages

- Loperamide 4mg PO x1, then 2mg after each loose stool. Maximum 16mg/day

Adverse Effects & Contraindications

- Adverse effects include distension, constipation, drowsiness, dizziness, fatigue, dry mouth, nausea and vomiting, and epigastric pain
- **Overuse** reported to result in **CNS depression** and **paralytic ileus**. This is most pronounced in individuals with **hepatic dysfunction** as first-pass metabolism of the drug may be decreased in these patients.
- The reduction of intestinal motility may be **deleterious** in diarrhea resulting from organisms in which exclusion of intestinal contents may be protective. Loperamide is CONTRAINDICATED in **acute diarrhea secondary to organisms which penetrate the intestinal mucosa** (*E. coli*, *Salmonella*, *Shigella*), or with **pseudomembranous colitis** (*C. difficile*).
- Caution in patients with **inflammatory bowel disease** as excessive use may lead to the development of **toxic megacolon.**

Practical Tips

- If clinical improvement not seen in **48 hours**, use should be **discontinued**.
- **Tolerance** to anti-diarrheal affects have been reported.
- 50 times more potent than morphine as an anti-diarrheal agent.
- Decrease dose in hepatic dysfunction.

"Errors in judgment must occur in the practice of an art which consists largely of balancing probabilities."

Sir William Osler. Teacher and Student, in Aequanimitas, 38.

Written by Marilyn Zeman; reviewed by Winnie Wong and Melissa Dutchak

Diphenoxylate/Atropine

Drug Class: synthetic phenylpiperidine (derivative opiate agonist), anti-diarrheal agent
Drug: **diphenoxylate/atropine** [Lomotil]

Mechanism of Action & Indications

- Combination of 2.5 mg of **diphenoxylate hydrochloride** and 0.025 mg of atropine sulfate.
- Diphenoxylate stimulates μ and δ **opiate receptors** of the bowel, resulting in a prolonged gastrointestinal transit time.
- Atropine's **anticholinergic effect** contributes slightly to the decreased gastrointestinal motility.
- Indicated as adjunctive agent in the treatment of mild or uncomplicated **travelers' diarrhea**.

Common Dosages

- Diphenoxylate/Atropine 1-2 tabs PO TID-QID

Adverse Effects & Contraindications

- Adverse effects may include **nausea**, **vomiting**, **abdominal discomfort**, **paralytic ileus**, **toxic megacolon**, **pancreatitis**, **sedation**, dizziness, pruritus, urticaria, lethargy, anorexia, restlessness or insomnia.
- Atropine component is associated with anticholinergic side effects, including **dryness of the skin** and mucosal membranes, **visual blurring**, thirst, hyperthermia, tachycardia, urinary retention and flushing.
- CONTRAINDICATED in diarrhea caused by enterotoxin producing bacteria, hypersensitivity to diphenoxylate or atropine, obstructive jaundice. Should not be used in individuals where reduction of intestinal motility could be deleterious.
- Avoid in patients with **acute ulcerative colitis** (may lead to toxic megacolon), **pseudomembranous colitis**, patients using **monoamine oxidase inhibitors** (may cause hypertensive crisis), and cases of **suspected poisoning or overdose**.

Practical Tips

- **Discontinue** if symptoms of diarrhea persist for more than **48 hours** or worsen.
- **Physical dependence** seen if given in large doses, with symptoms of **opioid withdrawal** after individual given large doses for extended periods (40-70 days).
- Acute toxicity causes a reaction similar to acute toxicity of **opiate analgesics** as well as symptoms of **atropinism**.
- Can **potentiate** the effects of other **CNS depressants** such as barbiturates, tranquilizers, and alcohol.
- Onset of initial response is within **30 to 60 minutes**, effect lasts for 3 to 4 hours.
- Careful in prescription writing, as many dispensing errors have occurred between **Lomotil** and **Lamictal**.
- **Naloxone** may be used as an antidote in Lomotil **overdose**.

"The human's "desire to take medicine" carries, however, a price tag. Nature's maladies are succeeded by iatrogenic hazards. Arising out of a restorative instinct, polypharmacy becomes itself an affliction."

Kurt Kroenke. Polypharmacy: causes, consequences, and cure. Am J Med. 1985; 79:149-52.

Written by Marilyn Zeman; reviewed by Winnie Wong and Melissa Dutchak

DYSPEPSIA, PEPTIC ULERS & ANTIEMETICS

H2-Receptor Blockers

Drugs: **cimetidine** [Tagamet], **famotidine** [Pepcid], **ranitidine** [Zantac], **nizatidine** [Axid]

Mechanism of Action & Indications

- **Inhibit acid production** by reversibly competing with histamine for binding of H2-receptors on the **basolateral** membrane of the parietal cell.
- Most prominent effect is on **basal acid secretion** with some effect on suppression of stimulated acid production.
- Particularly effective in suppressing nocturnal acid secretion (basal acid secretion). Therefore can heal **ulcers** by once daily dosing of H2-receptor blocker given between supper and bedtime.
- Also indicated in treatment of **dyspepsia**, **GERD**, **esophagitis**.
- Used for stasis **ulcer prophylaxis** in the ICU setting.

Common Dosages

- Famotidine 20-40mg PO qhs
- Ranitidine 150mg PO BID
- Cimetidine 300mg PO QID or 800mg PO qhs

Adverse Effects

- Overall incidence of adverse effects is low (<3%). Side effects include **infectious diarrhea (double risk)**, **headaches**, **drowsiness**, fatigue, muscular pain, and constipation.
- Less commonly, may have **CNS effects** such as confusion, delirium, hallucinations, slurred speech, and headaches (usually occurs with intravenous administration of the drugs).
- With cimetidine, gynecomastia in men and galactorrhea in women may occur due to binding to androgen receptors and inhibition of estradiol hydroxylation. Also, some reduction in sperm counts and reversible impotence have been seen.

Practical Tips

- Some patients treated with proton pump inhibitors may benefit from a **H2-receptor antagonist** at night if they have **nocturnal acid breakthrough**.
- Only 10-35% undergo metabolism of the liver. Both metabolized and unmetabolized products are excreted by the **kidney** by both tubular filtration and renal tubular secretion. It is therefore important to reduce doses of H2-receptor antagonists in patients with a reduced creatinine clearance.
- **All agents that inhibit gastric acid secretion** may decrease absorption and bioavailability of H2-receptor antagonists.
- Drug interactions mainly reported with **cimetidine** as it inhibits **cytochrome P450 enzymes** more so than other H2-receptor blockers.
- **Cimetidine** may **reduce tubular secretion** of **creatinine**, causing a small but significant increase in serum creatinine in the absence of decreased glomerular filtration rate. Cimetidine can also inhibit renal tubular secretion of **procainamide**.

Written by Marilyn Zeman; reviewed by Winnie Wong and Ihor Pecuh

Proton Pump Inhibitors (PPIs)

Drugs: **esomeprazole** [Nexium], **lansoprazole** [Prevacid], **omeprazole** [Losec], **pantoprazole** [Pantoloc], **rabeprazole** [Pariet]

Mechanism of Action & Indications

- All proton pump inhibitors are "**prodrugs**", requiring activation in the acidic environment of the stomach. They enter the **parietal cells from the blood** and accumulate in the cell's acidic secretory canaliculi.
- **Directly inhibit gastric acid secretion** by binding irreversibly and inhibiting the **H/K-ATPase** pump causing **hypochlorhydria**.
- Omeprazole also **selectively inhibits gastric mucosal carbonic anhydrase**, which may contribute to its action.
- Useful for treatment of **ulcers**, **dyspepsia**, **GERD**, **esophagitis**. Also combined with antibiotics for ***H. pylori* eradication**.
- May be used for stasis ulcer prophylaxis in the ICU setting as well.

Common Dosages

- Esomeprazole 20-40mg PO daily
- Lansoprazole 15-30mg PO daily
- Omeprazole 20-40mg PO daily
- Pantoprazole 40mg PO/IV daily-BID for most indications. However, for active non-variceal upper GI bleeds secondary to ulcers, the dose is 80mg IV bolus, then 8mg/hour for 72 hours.
- Rabeprazole 20mg PO daily

Adverse Effects

- Adverse effects are usually few, but may include **nausea**, **abdominal pain**, **constipation**, flatulence and diarrhea. Subacute myopathy, arthralgias, headaches and skin rashes have also been reported.
- **Hypergastrinemia** (>500ng/L) occurs in 5-10% of **long-time omeprazole** users. Development of hypergastrinemic state predisposes the patient to rebound hypersecretion of gastric acid following discontinuation of therapy. There is also a theoretical concern that elevated gastrin levels could promote tumors of the GI tract.
- **Chronic treatment** with proton pump inhibitors may **decrease iron absorption** due to acid suppression. In addition, omeprazole has been found to decrease the absorption of **vitamin B12**, although its clinical significance is uncertain.
- Potentially increased risk of ***C. difficile* colitis** and aspiration **pneumonia**.

Practical Tips

- Requirement for **acid to activate drugs** means that PPIs should be taken **before meals.** Incorrect timing of administration is the most common reason of PPI failure.
- **Co-administration** of other acid-suppressing, such as H2-receptor antagonists may **diminish** the **efficacy** of the proton pump inhibitor.
- If given in sufficient doses regularly, can **reduce daily gastric acid secretion** by **>95%**.
- With once a day dosing, **steady state inhibition** may take **2-5 days**. However, **pantoprazole**, at a single IV bolus of 80mg can **inhibit acid production by 80-90% within one hour**. This effect can last up to 21 hours.
- Rapidly absorbed, highly protein bound and metabolized by cytochrome P450 system (particularly CYP2C19 and CYP3A4).
- Chronic renal or liver failure do not lead to drug accumulation with once-a-day dosing. **Hepatic disease** however **reduces the clearance of lansoprazole** substantially; therefore, lansoprazole dose may need to be reduced in patients with severe hepatic disease.
- Inhibit the activity of some **cytochrome P450 enzymes**, and therefore decrease the clearance of benzodiazepines, warfarin, phenytoin and others.
- Toxicity has been reported with **disulfiram**.

Written by Marilyn Zeman; reviewed by Winnie Wong and Ihor Pecuh

Dimenhydrinate

Drug Class: antihistamines, anti-emetics
Drug: **dimenhydrinate** [Gravol]

Mechanism of Action & Indications

- Dimenhydrinate is made up of **diphenhydramine** (active moiety) and chlorotheophylline.
- It has **antihistaminic** and **anticholinergic** properties and is known as an **anti-vertigo** and **antiemetic** agent.
  - Through its **anticholinergic** effect, it depresses vestibular stimulation and inhibits the stimulation of the labyrinthine (precise mechanism unknown).
  - Its **peripheral anticholinergic** effects contribute to its anti-motion sickness effects.
  - **Inhibits** at the synapses in the **vomiting centre** (precise mechanism unknown).

Common Dosages

- Dimenhydrinate 25-50mg PO/IV/SC q4h prn

Adverse Effects & Contraindications

- Can cause **dizziness**, **sedation** (particularly with alcohol or other CNS depressants) and more importantly, **syncope**, **hypotension** and **confusion** in the elderly. In addition can cause hallucinations, seizures, and palpitations.
- Multiple GI effects including **epigastric pain**, **anorexia**, diarrhea or constipation and even nausea and vomiting.
- Through its anticholinergic and antihistamine effects, may cause **blurring of vision**, **dryness of mouth**, nose and throat, as well as **urinary hesitancy and retention**.
- Can cause photosensitivity, urticaria, drug rash as well as anaphylaxis and hemolytic anemia.
- Caution in narrow-angle glaucoma, stenosing peptic ulcer disease or pyloroduodenal obstruction, symptomatic prostatic hypertrophy, bronchial asthma, bladder neck obstruction, cardiac arrhythmias, pregnancy (i.e. any condition in which an anticholinergic is contraindicated).

Practical Tips

- Antiemetic effects occur within **15-30 minutes** following oral intake and immediately after intravenous injection.
- Some **decreases** in the antiemetic **efficacy** may occur after **prolonged** use. **Tolerance** may also occur to the CNS depressant effects.
- Although used to treat hyperemesis gravidarum, does cross the placenta (**class B**).
- Serious sedation if used with **alcohol** or **other CNS depressants**.
- Hepatic half-life unknown but diphenhydramine is extensively metabolized by the liver and excreted as metabolites in the urine within 24 hours. Elimination half-life approximately 3.5 hours.

"The best doctors in the world are Dr. Diet, Dr. Quiet and Dr. Merryman."

Jonathan Swift

Metoclopramide

Drug Class: prokinetic agents, anti-emetics
Drug: **metoclopramide** [Maxeran]

Mechanism of Action & Indications

- Facilitates **acetylcholine release** from enteric neurons through the **antagonism of 5-HT3 receptors** and stimulation of excitatory neurons via activation of 5-HT4 receptors.
- Also **inhibitory effects on dopamine** via dopamine D2 receptor on cholinergic enteric neurons.
- Has both **central** and **peripheral** anti-dopaminergic effects which leads to **anti-nauseant and anti-emetic effects**, and **prokinetic effects**, respectively.
- Indicated for symptomatic patients with **gastroparesis**, with mild-moderate improvement in gastric emptying.
- Has been used in patients with **GERD**, producing symptomatic relief without promoting healing of ulcers.
- Particularly useful for management of **nausea symptoms when starting opioids**.
- Also used in the treatment of **persistent hiccups**, but efficacy is equivocal at best.

Common Dosages

- Metoclopramide 5-10mg PO/IV/SC q4h prn

Adverse Effects

- Although rare, side effects may be serious and include **extrapyramidal effects**. **Dystonia** usually occurs acutely after intravenous administration and **parkinsonism-like** symptoms may occur several weeks after initiation of therapy.
  - Extrapyramidal effects respond to treatment with **anticholinergics** or **antihistaminic drugs** and are **reversible** with discontinuation of the drug.
  - **Tardive dyskinesia** can occur with chronic treatment (months to years) and may be **IRREVERSIBLE**.
- Can also infrequently cause **galactorrhea**, like other dopamine antagonists.

Practical Tips

- Usually given 30 minutes before meals and at bedtime.
- Use with **caution** in patients with **renal impairment**.
- As metoclopramide enhances gastric and small bowel motility, it may decrease the gastric absorption and **increase the small bowel absorption** of **sustained-release or enteric coated drugs**.
- Limited effect on improving transit time with small bowel motility disorders.
- In patients with severe nausea can be given **intramuscularly** (onset 10-15 min) or **intravenously** (onset 1-3 min). Infusion can be given in individuals undergoing chemotherapy.
- Rapidly absorbed after oral ingestion and is sulfated and undergoes glucuronide conjugation by the liver. It is excreted principally in the **urine**, with a **duration of action of 1-2 hrs**.

"The art of medicine consists in amusing the patient while nature cures the disease."

Voltaire

Domperidone

Drug Class: D_2 dopaminergic receptor antagonists, prokinetics, anti-emetics
Drug: **domperidone** [Motilium]

Mechanism of Action & Indications

- Domperidone blocks peripheral dopamine receptors resulting in **gastric peristalsis** and **lowering of the esophageal sphincter pressures**. This then causes increased gastric emptying and decreased small bowel transit time (prokinetic).
- Its antiemetic properties are the result of **blocking dopamine receptor** at the chemoreceptor trigger zone as well as at the gastric level.
- Indicated for treatment of **GI motility disorders**, **GERD**, and sometimes for **nausea and vomiting**.

Common Dosages

- Domperidone 10-20mg PO TID-QID

Adverse Effects & Contraindications

- **Galactorrhea**, **gynecomastia**, **mastalgias**, **hot flushes** or **menstrual irregularities** through increased **prolactin** levels.
- CNS effects are rare as domperidone **penetrates the blood-brain barrier poorly** (unlike metoclopramide) but may include dry mouth and headache.
- Rarely causes **asthenias**, **extrapyramidal effects**, lethargy, dizziness, irritability, nervousness or thirst. Extrapyramidal side effects usually **resolve spontaneously** when treatment is discontinued.
- When given intravenously (this form is not available in Canada), possible effect of **QT prolongation** and therefore risk of causing torsades of pointes.
- Increases prolactin levels. Do not use in patients with a prolactinoma.

Practical Tips

- Should not be used if there is a suspicion of mechanical obstruction or perforation, GI bleed or any hepatic impairment.
- As domperidone enhances gastric and small bowel motility, it may decrease the gastric absorption and **increase the small bowel absorption** of **sustained-release or enteric coated drugs**.

Advanced Tips

- Usually given 30 minutes before meals and at bedtime.
- Very highly protein bound and therefore **does not readily cross the blood-brain barrier**.
- Reaches **peak concentrations within 30 minutes** of dosing and undergoes extensive first pass metabolism through **CYP3A4**.
- Studies indicate that it may be used to treat **migraines** in "dopamine sensitive" individuals.

Written by Marilyn Zeman; reviewed by Winnie Wong and Ihor Pecuh

Serotonin Receptor Antagonists

Drugs: **dolasetron** [Anzemet], **granisetron** [Kytril], **ondansetron** [Zofran]

Mechanism of Action & Indications

- Competitively inhibit the action of **serotonin (5-HT3)**, which is normally released by enterochromaffin cells of the small intestine in response to various stimulants (e.g. chemotherapeutic agents). This leads to decreased binding of 5-HT3 receptors, and subsequent **reduced vagal afferents** to activate the nausea/vomiting reflex.
- Used most commonly as **treatment or prophylaxis** for **chemotherapy-induced nausea** or nausea secondary to **upper abdominal irradiation**.
- Has an important role in **intractable nausea and vomiting** from other causes. Effective against **hyperemesis of pregnancy** and **postoperative nausea**.

Common Dosages

- Granisetron 2mg PO daily
- Ondansetron 4-8mg PO/IV q8h prn

Adverse Effects

- Very well tolerated. Most common affects include **constipation**, **diarrhea**, **headaches** and **light-headedness**.
- Experimentally found to induce minor ECG changes which are not felt to be clinically significant in most cases.

Practical Tips

- Well absorbed from GI tract and metabolized by the liver by several **cytochrome P450 pathways**.
- Patients with **liver dysfunction** therefore have a **reduced** plasma clearance of the drug, and dose adjustment is therefore advised.
- Some reduction has also been found with ondansetron clearance in the **elderly**, but no dose adjustment is recommended with age.
- Very **effective** and very **expensive** relative to other anti-emetic agents.
- **Not effective** against **motion sickness**.

"Drug companies… find out who their markets are early—in medical school—and they stay with them until they retire."

Dr. Arthur L. Caplan. On favoritism behind the high costs of drugs. LA Times 11 Apr 91.

BLOOD PRODUCTS & HEMATINICS

General Principles of Transfusion

- Efforts should be made to minimize blood loss and utilize conservation strategies to **reduce** patient needs for transfusion. Transfusion should be prescribed only when the **benefits** are **clearly greater** than the **risks**.
- Given the risks associated with blood product transfusion, **informed consent** is always required from either the patient or his/her surrogate prior to administration.
- The major risks associated with blood product transfusion are outlined in Table 1.
- Blood product compatibility for various blood groups is outlined in Table 2.

Table 1. Blood Product Transfusion Risks

Non-Infectious Risks		Risk per Unit of PRBC or Platelet Pool Transfused
Acute Hemolytic Reaction		1:12,500
Fatal Acute Hemolytic Reaction		1:600,000
Delayed Hemolytic Reaction		1:9,000
Allergic		PRBC 1:250; platelet pool 1:25
Febrile Non-Hemolytic Reaction	Red Blood Cells	1:500
	Platelets	1:15
Transfusion Related Acute Lung Injury (TRALI)	Red Blood Cells	1:71,500
	Platelets	1:8,300
Anaphylaxis	Red Blood Cells	1:23,2500
	Platelets	1:1,600
Circulatory Overload	Red Blood Cells	1:2,400
	Platelets	1:5,950
Infectious Risks		
Viral	HIV	1:4.7 – 10 million
	HBV	1:72,000 but only 1:1.4million chronic HBV
	HCV	1:3.1 million
	HTLV-1&II, HAV, WNV, EBV, CMV	Rare
	HPV-B19	Very Rare
Bacterial	Sepsis	1:2,500–12,000 with platelets; <1:1 million fatal with red cells
	Syphilis	Very Rare
Parasites	Malaria	1:4 million
	Babesiosis, Chagas's disease, Leishmaniasis	Rare
Prions	CJD; vCJD	Theoretical risk only

Table 2. Blood Product Compatibility

Recipient Blood Type	Donor Blood Type		
	Red cells	Platelets	FFP
Group O	O	O,A,B,AB	O,A,B,AB
Group A	A,O	A,AB	A,AB
Group B	B,O	B,AB	B,AB
Group AB	AB,A,B,O	AB	AB

Written by Randy Chung; reviewed by Anthony Woods and Susan Nahirniak

Packed Red Blood Cell Transfusion

Mechanism of Action & Indications

- Packed red cells are given to replace blood loss in **acute bleeds**, increasing the oxygen carrying capacity of the recipient's blood.
- Indications for transfusion

Hemoglobin	Recommendation for transfusion
>100g/L	Inappropriate except in exceptional circumstances
70-100g/L	Appropriate if signs or symptoms of impaired oxygen delivery were present
<70g/L	Likely appropriate
<60g/L	Transfusion recommended

Common Dosages

- In non-urgent settings, red cells should be administered **1-2 units** at a time.
- Each unit must be infused within 4 hours of spiking. In non-urgent settings, each unit is typically infused over 2 hours.

Adverse Effects & Contraindications

- The major non-infectious adverse effects of blood transfusion include **acute hemolytic reactions**, **febrile non-hemolytic reactions**, **transfusion related lung injury**, **allergic reactions**, **septic reactions** and **circulatory overload**.
- The major infectious risks include transmission of **HIV, HBV, HCV**, bacteria, and possibly prions.

Practical Tips

- Patients should be **re-assessed clinically** and the hemoglobin level **re-checked** prior to transfusing additional units.
- One unit of red cells should raise the Hb by **10g/L** in the absence of ongoing bleeding, sequestration, or destruction.
- Consider diuresis with **furosemide 20mg IV after each unit of pack cell** transfusion in most patients except those with significant intravascular fluid depletion.
- One unit of red cells is derived from 450±70ml of whole blood to create a packed red cell of ~280-300ml with a hematocrit of 55-60%.

"Whether they admit it as much or denied it, they all without exception in the depths of their hearts believed that there was a doctor, or a herbalist, or some old witch of a woman somewhere, whom you only had to find and get that medicine…to be saved…. It just wasn't possible that their lives were already doomed. However much we laugh at miracles when we are strong, healthy and prosperous, if life becomes so hedged and cramped that only a miracle can save us, then we clutch at this unique, exceptional miracle and--believe in it!"

Solzhenitsyn, Alexander. Cancer Ward. New York; Modern Library; 1968, p. 143.

Written by Randy Chung; reviewed by Anthony Woods and Susan Nahirniak

Platelet Transfusion

Mechanism of Action & Indications

- Platelets are given in bleeding secondary to thrombocytopenia or platelet dysfunction. General guidelines for providing platelet transfusion are outlined in the following table:

Indications	Platelet Transfusion Threshold
Neurosurgery, CNS trauma	$< 100\times10^9$/L
Epidural catheter insertion or removal	$< 50\times10^9$/L
Surgery, Lumbar puncture, significant microvascular bleeding, vaginal bleeding	$< 50\times10^9$/L
Thrombocytopenia with fever or coagulopathy, critically ill patients	$< 20\times10^9$/L
Thrombocytopenia with marrow failure	$< 10\times10^9$/L

- There are three types of platelets—(1) pool of 4 buffy coat derived platelets, (2) apheresis single donor platelets, and (3) HLA matched single donor platelets (for refractory patients).

Common Dosages

- A standard adult dose is either **one buffy coat pool** or **one apheresis platelet**. Both contain ~3.0×10^{10} platelets in ~300ml of plasma.

Adverse Effects & Contraindications

- Platelet transfusion is CONTRAINDICATED in **thrombotic thrombocytopenic purpura** (TTP), **hemolytic uremic syndrome** (HUS) and **heparin-induced thrombocytopenia** (HIT) except where life or limb is threatened by hemorrhage. Platelet transfusion is associated with exacerbation of TTP/HUS and arterial thrombosis in HIT.
- Platelet transfusion is relatively contra-indicated in **immune thrombocytopenia purpura** (ITP) except where life or limb is threatened by hemorrhage. Platelet transfusion alone is often ineffective in ITP. In the rare circumstance when platelet transfusion is required, corticosteroids and/or IVIG should be administered concomitantly to enhance platelet survival.
- Specific risks of platelet therapy include **bacterial contamination**, **alloimmunization**, **febrile transfusion reactions**, and **plasma reactions**.

Practical Tips

- Establishing the **etiology** of thrombocytopenia is imperative prior to platelet transfusion (see adverse events and contra-indications).
- One standard adult dose should raise the platelet count of a 70kg adult by 2.5-5×10^9/L in the absence of ongoing platelet consumption, sequestration, or destruction.
- Serious spontaneous bleeding is unlikely to occur at platelet counts **$>10\times10^9$/L**.
- A **post transfusion platelet count** obtained 15 minutes to 1 hour following infusion of platelets is required before patient can be worked up and registered for **HLA matched platelets**.

Written by Randy Chung; reviewed by Anthony Woods and Susan Nahirniak

Fresh Frozen Plasma (FFP) and Cryoprecipitate

Mechanism of Action & Indications

- FFP is separated from whole blood and frozen within 8 hours to preserve chiefly the **labile proteins**.
- Cryoprecipitate represents a specific protein subset of FFP that remain insoluble when FFP is frozen and then thawed to 40°C, including **fibrinogen**, factor VIII, vWF, factor XIII, and fibronectin.
- FFP is given to replace coagulation factors in **multifactorial deficiencies**, such as **dilutional coagulopathy**, **liver disease with bleeding**, **warfarin reversal**, **factor deficiency**, **disseminated intravascular coagulopathy**, and **replacement for plasmapheresis**.
- In contrast, cryoprecipitate should be considered if fibrinogen is disproportionally low in comparison to other coagulation factors. **Adjuvant use** of cryoprecipitate is indicated in bleeding patients with fibrinogen levels **<1.0g/L**.

Common Dosages

- Each unit of FFP is not concentrated and has a volume of 225ml; dosing is guided by coagulation testing, however, a typical dose is **10ml/kg**. Most recommend **2 units at a time, then re-evaluate.**
- One unit of cryoprecipitate contains 150mg fibrinogen; usual dose is **6 units** (**~1 unit/10kg**) **of cryoprecipitate** thereby delivering approximately 2 g fibrinogen.
- Recommended infusion times are 30-120min/unit of fresh frozen plasma (maximum 4 hours), and 10-30min/dose (maximum 4 hours).

Adverse Effects

- Specific risks of plasma therapy include **anaphylaxis**, **viral transmission**, and **transfusion related acute lung injury**.

Practical Tips

- Coagulation studies can be measured 15 minutes post transfusion to determine the effect of FFP or cryoprecipitate.
- Administration of further products to bleeding patients should be guided by **serial coagulation testing**, including **fibrinogen levels**.
- FFP contains significant amounts of **all clotting factors**, **both pro- and anticoagulant**, including fibrinogen. However, levels of the labile proteins (factor V and factor VIII) diminish rapidly, even under refrigeration.

"The philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow."

Osler, William. Aequanimitas, with Other Addresses to Medical Students, Nurses, and Practitioners of Medicine, 3rd ed. Philadelphia: Blakiston's Son; 1932, p. 266.

Written by Randy Chung; reviewed by Anthony Woods and Susan Nahirniak

Iron

Drug Class: elemental supplement

Drugs:

- Oral—**ferrous fumarate** [Palafer], **ferrous sulphate**, **ferrous gluconate**
- **Intravenous—iron dextran** [Dexiron], **iron sucrose** [Venofer], **ferrous gluconate** [Ferrlecit]

Mechanism of Action & Indications

- Iron is an essential component of **heme**, which is required for **hemoglobin** and thus **erythrocyte production**.
- Indicated for **iron deficiency anemia** and **anemia from chronic renal failure with combined iron deficiency**. Should be considered in **all** pregnant women.

Common Dosages

- Ferrous fumarate 300mg (100mg elemental iron) PO BID
- Ferrous gluconate 300mg (35mg elemental iron) PO BID-TID
- Ferrous sulphate 300mg (60mg elemental iron) PO BID-QID
- Ferrous sulphate liquid 10ml (30mg/ml, 6mg/ml elemental iron) PO BID-QID
- Iron sucrose 5ml (100mg elemental iron) IV 1-3x/week (usually with dialysis)

Adverse Effects & Contraindications

- May cause **constipation**, **diarrhea** or **dark stools**. The dark stool may mimic melena. Iron therapy tends to lower both false-positive and false-negative results for fecal occult blood testing.
- Oral liquid iron can **stain the skin**. In addition, it can **stain the teeth**.
- Intramuscular iron can cause staining of the skin and injections are very painful.
- Intramuscular or intravenous **iron dextran** can cause **anaphylaxis** (to dextran). Thus, always use a **test dose** prior to administration and be prepared for **anaphylaxis**.
- **Acute reactions** of **fever**, **arthralgia**, **myalgia**, and **nausea** could occur during administration and up to 48 hrs after administration of intravenous or intramuscular iron. These reactions are much more common than anaphylactic reactions.
- Can lead to **iron overload** when used in excess, especially in susceptible patients (**hemochromatosis** and patients requiring repeated transfusions e.g. **thalassemia**).
- CAUTION: only use iron supplements in patients with documented iron deficiency or at risk of iron deficiency. **STOP** the iron supplement when it **is no longer required**.

Practical Tips

- In cases of documented iron deficiency, supplementation should continue until the **hemoglobin has normalized** AND **iron stores have been replenished** (i.e. **ferritin>50**). This often takes 6 months or longer.
- Before prescribing iron always consider **other causes of microcytosis**, especially where the patient might have normal or increased iron stores. For example, anemia of chronic disease, thalassemia, and sideroblastic anemia.
- In **males** and **post menopausal females**, only use with documented deficiency as they are at risk for iron overload.
- **Parenteral iron** must be reserved for patients who cannot take oral iron.
- In the **elderly**, ferrous sulphate exceeding 325mg (elemental iron of 65mg) is seldom needed and may lead to **constipation**.
- It is preferable to take **oral iron before or two hours after meals**. To improve tolerance, it may be taken with meals but this will reduce absorption by up to 50%.
- **Slow release and enteric coated preparations** are much **more expensive** and offer no advantage as most iron is absorbed in the proximal small intestine.
- Iron deficiency is due to a **deficient intake**, **absorption** and/or **increased loss**. **ALWAYS** rule out blood loss.
- **Achlorhydria** and **drugs that reduce gastric acidity** will reduce iron's oral absorption.
- **Antacids** and **phosphate binders** can reduce absorption of oral iron.

Written by Peter Hamilton; reviewed by Alan McMahon and Gregg Holowaychuk

Recombinant Human Erythropoietins

Drugs: epoetin alfa [Eprex], **darbepoetin alfa** [Aranesp]

Mechanism of Action & Indications

- Stimulates the **division and differentiation** of committed red blood cell precursors and release of reticulocytes from the marrow.
- Used for the treatment of **anemia** associated with **chronic kidney disease (Hb<110g/L)** and **HIV (AZT treated)**.
- Also indicated in **preoperative autologous blood collection** and anemic patients with **non-myeloid malignancies (Hb<100g/L)** in whom blood transfusions are not feasible (transfusion reaction, cross-matching difficulties, or iron overload).

Common Dosages

- Epoetin alfa 50-150units/kg SC/IV 3 times/week for renal failure.
- Epoetin alfa 30,000-40,000units SC/IV once/week for malignancy.
- Darbepoetin alfa 0.45 μg/kg SC/IV weekly. Initial dose in patients on chemotherapy 2.25 μg/kg SC/IV weekly.

Adverse Effects & Contraindications

- **Hypertension** is common (manage hypertension before starting), particularly in patients with chronic renal failure.
- **Pure red cell aplasia** with SC administration of **epoetin**. Rarely reported with darbepoetin.
- **Venous thromboembolism** (particularly in patients with preexisting malignancy) and excessive hematocrit.
- Headache and GI upset.

Practical Tips

- Additional **causes of anemia** (e.g. blood loss, hemolysis, hematinics) should always be **ruled out** prior to initiating therapy.
- In patients with **end-stage kidney disease**, absolute iron deficiency is likely if ferritin <100 or transferrin saturation <20%. **Concurrent therapy with iron supplementation** is recommended.
- Evaluate initial response every two weeks, titrating Hb to 110-120g/L.
  - A clinical response may be anticipated in **2-4 weeks**.
  - For chronic kidney disease, reduce the dose if Hb>120g/L
  - For non-myeloid malignancies, erythropoietin should be discontinued if Hb exceeds 120g/L until it falls below 100g/L, and restarted at a dose 25% below the previous dose. If Hb is rising by more than 20g/L per month, the dose should be reduced by about 25%.
- Erythropoietin levels **>500mU/ml** predicts a poor response to erythropoietin.

"This is all very fine, but it won't do--anatomy, botany. Nonsense, Sir! I know an old woman in Covent Garden who understands botany better, and as for anatomy, my butcher can dissect a joint full as well. No, young man, all this is stuff: you must go to the bedside, it is there alone you can learn disease."

Sydenham, Thomas. Dewhurst K, Dr. Thomas Sydenham (1624-1689): His Life and Original Writings. Los Angeles: University of California Press; 1966, p. 48.

Written by Dominic Carney; reviewed by Loree Larratt

ANTICOAGULANTS

Unfractionated Heparin (UFH)

Drug Class: anticoagulants
Drug: unfractionated heparin (UFH)

Mechanism of Action & Indications

- Heparin **reversibly** binds to **antithrombin (AT III)** and increases the rate at which it inactivates **most activated clotting factors, particularly thrombin and factor Xa**. Thrombin inactivation **inhibits fibrin clot formation** and also **thrombin-induced activation of platelets and factors V and VIII**.
- Indicated for **prophylaxis** (e.g. major surgery, certain medical inpatients) and **initial treatment** (e.g. DVT, PE, unstable angina, acute MI) of thromboembolic disorders.

Common Dosages

- For DVT prophylaxis, unfractionated heparin 5000 units SC BID.
- Please refer to other hospital resources for therapeutic doses. These vary with indication.

Adverse Effects

- **Hemorrhage** is the most common adverse effect of heparin, particularly with the larger doses used for therapy. There are many causes of increased risk of bleeding (e.g. **bleeding disorder, recent GI or intracerebral bleed**). Risk increases with aPTT ratios above the recommended target range.
- **Immune mediated heparin-induced thrombocytopenia** (HIT) may be associated with clinically important thrombosis.
- **Osteoporosis** with long-term use.
- Increase in AST and ALT may occur, are usually transient and of no consequence.
- **Local skin reactions**, hypoaldosteronism, alopecia. Hypersensitivity reactions are rare.

Practical Tips

- UFH for **therapy** is usually given by **continuous IV infusion**.
- UFH for **prophylaxis** is usually **administered subcutaneously**.
- IM administration should be avoided.
- Obtain baseline **CBC, PT, aPTT and platelet** count prior to initiation of therapy. **Monitor platelet counts every other day until day 14 or discontinuation of heparin**, whichever occurs first.
- For treatment, body weight based dosing is usually used. The **aPTT** is the most common test used to monitor anticoagulant effect. It should be measured **6 hours after a bolus dose of heparin, and thereafter as needed**. The dose is adjusted according to the results.
- The anticoagulant effects of UFH may be **neutralized by protamine sulphate**. One milligram of protamine neutralizes 100 units of UFH.
- Concomitant use of other anticoagulants or antiplatelet agents increases bleeding risk.

Written by Jeff Whissell; reviewed by Michael Mant and Dayle Strachan

Advanced Tips

- **Heparin-Induced thrombocytopenia (HIT) – immune mediated**
  - Minor non-immune mediated decreases in platelet count are common in the first few days of therapy, platelets recover within 4 days of continued heparin; is usually of no importance. However, **immune mediated thrombocytopenia**, with an incidence of up to **3%**, is important.
  - HIT should be suspected when the platelet count falls **below normal or by 50%**, without other obvious cause, usually between **days 4 to 14 of therapy**. Heparin exposure within the previous 3 months may be followed by rapid-onset HIT within 24 hours of re-exposure. Delayed HIT, beyond 14 days, has occasionally been described.
  - **50%** of patients will develop **venous or arterial thromboembolism**.
  - A definitive diagnosis is made with a **positive HIT assay**.
  - When HIT is suspected, **all forms of heparin and LMWH, including heparin flushes**, should be immediately discontinued. Therapeutic doses of a non-heparin anticoagulant (e.g. lepirudin, argatroban, danaparoid) should be instituted. The **thrombocytopenia usually corrects within a few days**. However, the **risk of thrombosis persists for up to 30 days**.
  - Warfarin should **not** be administered on its own in these patients. Vitamin K should be administered to patients receiving warfarin at the time HIT develops. **Warfarin** initiation should be **deferred** until the **platelet count is >100 x 10^9/L** and while patient continues an alternate parenteral anticoagulation.
  - Prophylactic platelet transfusion is not recommended. Very rarely, platelets may be indicated for potentially life-threatening hemorrhage.

"Formerly, when religion was strong and science weak, men mistook magic for medicine; now, when science is strong and religion weak, men mistake medicine for magic."

Thomas Szasz, The Second Sin (1973) "Science and Scientism".

Low Molecular Weight Heparin (LMWHs)

Drug Class: anticoagulants

Drugs: **dalteparin** [Fragmin], **enoxaparin** [Lovenox], **nadroparin** [Fraxiparin], **tinzaparin** [Innohep]

Mechanism of Action & Indications

- LMWHs **reversibly bind to antithrombin (AT III)**, in a similar fashion to UFH. As compared to UFH, the degree of inhibition of thrombin is less than that of factor Xa. The aPTT is minimally affected and is not used to monitor therapeutic response.
- Indicated in the **prophylaxis** (e.g. major surgery, certain medical inpatients) and **initial treatment** (e.g. DVT, PE, unstable angina, acute MI) of thromboembolic disorders.

Common Dosages

- Dalteparin
  - DVT prevention after general surgery: 2500 units SC 1-2 hours before surgery, then SC daily
  - DVT prevention after surgery associated with other risk factors/orthopedic: 5000 units SC given the evening prior to surgery, then 5000 units SC daily thereafter OR 2500 units SC 1-2 hours before surgery and 8-12 hours later, then 5000 units SC daily on the following days
  - Treatment of VTE: 200 units/kg SC daily
- Enoxaparin
  - DVT prevention after orthopedic surgery: 30mg SC every 12 hours beginning 12-24 hours after surgery
  - DVT prevention after abdominal/colorectal surgery: 40mg SC daily beginning 2 hours prior to surgery
  - DVT prevention in medical patients: 40mg SC daily
  - Treatment of VTE: 1mg/kg SC every 12 hours (best for higher risk patients) or 1.5mg/kg SC daily
- Nadroparin
  - DVT prevention after general surgery: 2850 units SC daily beginning 2-4 hours before surgery and continuing for 7 days, or longer
  - DVT prevention after hip replacement: 38 units/kg SC 12 hours before surgery, 12 hours after surgery and continuing daily for 3 days, then increased to 57 units/kg SC daily for days 4 through 10, or longer
  - Treatment of VTE: 171 units/kg SC daily (recommended max of 17,100 units per day) or 86 units/kg SC q12h (if at increased risk of bleeding)
- Tinzaparin
  - DVT prevention after general surgery: 3500 units SC given 2 hours before surgery, then daily for 7-10 days, or longer
  - DVT prevention after orthopedic surgery: 50-75 units/kg (weight based) SC 2 hours before surgery, then daily for 7-10 days, or longer
  - Treatment of VTE: 175 units/kg SC daily (recommended max of 18,000 units per day)

Adverse Effects & Contraindications

- The most common adverse effect is **hemorrhage** (see UFH).
- Rare cases of **intra-spinal hematoma** with **concurrent use of spinal/epidural anesthesia or puncture** resulting in long-term permanent paralysis have occurred.
- Other adverse effects include asymptomatic elevation of liver enzymes, weak osteopenic effect and immune-mediated heparin induced thrombocytopenia (HIT).
- Use with **caution** in patients with **hepatic or renal insufficiency**. Avoid LMWH if **creatinine clearance is <30 ml/min**, use UFH instead.
- Because of the long half lives of LMWHs, **avoid** use in patients at **high risk for acute bleeding**. Use unfractionated heparin instead.

Written by Jeff Whissell; reviewed by Michael Mant and Dayle Strachan

Practical Tips

- HIT can occur with LMWHs, although less frequently than with UFH. LMWHs should **never** be used as an **alternate anticoagulant to UFH in patients with suspected HIT**.
- Periodic complete blood counts (e.g. every 2-3 days) including platelet count are recommended when practical early during treatment.
- LMWH dose is fixed and anticoagulant monitoring is not routinely required. However, **anti-Xa levels** are recommended in **children**, **pregnant patients**, the **morbidly obese**, the **very small** adult, and those with **renal insufficiency**. The blood sample should be drawn 4 hours following a third or fourth therapeutic dose. Monitoring is by anti Xa levels. Proposed therapeutic values vary with the LMWH used.
- **Protamine sulphate** will neutralize **only some** of the anticoagulant activity of LMWHs.
- Concomitant use of other anticoagulants or antiplatelet agents increases bleeding risk.

"Whenever the illness is too strong for the available remedies, the physician surely must not expect that it can be overcome by medicine. To attempt futile treatment is to display an ignorance that is allied to madness."

Hippocrates. A Graceful Exit: Life and Death on Your Own Terms. New York; Insight Books, Plenum Press; 1996.

Warfarin

Drug Class: anticoagulants
Drug: warfarin [Coumadin]

Mechanism of Action & Indications

- Inhibits the **vitamin K-dependent** hepatic synthesis of **coagulation factors II, VII, IX, & X**.
- Also inhibits hepatic synthesis of the naturally occurring anticoagulants protein C and protein S.
- Indications include **atrial fibrillation**, **cardioembolic stroke**, **prosthetic heart valves** and **venous thromboembolism**.

Common Dosages

- Usually initiate patients with 5-10 mg daily for 3 days. Then adjust dose based on INR.
- For those who are elderly, debilitated, malnourished, have liver disease or are on medications known to increase the INR, use starting dose of <5mg.
- The average daily maintenance dose is 4 to 5 mg; however, considerable individual variability exists.
- It takes an average of 5 to 7 days for patients to reach a therapeutic INR. If crossing the patient over from UFH or LMWH, discontinue these agents after the INR has been at a therapeutic level for 2 days and a minimum of 5 days heparin has been given.

Adverse Effects & Contraindications

- As with all anticoagulants, hemorrhage is the most common adverse effect. Risk increases with the INR. Other adverse effects are uncommon, including skin necrosis, purple toes, alopecia, agranulocytosis, etc.
- Warfarin is a known teratogen. Appropriate birth control measures are recommended in women of childbearing age.
- Cautions/contraindications:
  - Current or high risk of serious bleeding or serious injury.
  - Spinal puncture, surgery and other procedures with the potential for uncontrolled bleeding.
  - Patients who are unwilling or unable to have necessary INR monitoring.

Practical Tips

- Monitoring and target range:
  - Patient education is very important.
  - For most indications, a target INR of 2.5 is recommended, with an acceptable range of 2.0 – 3.0.
  - For patients with some mechanical heart valves, a target INR of 3.0 with range of 2.5 – 3.5 is indicated.
  - When initiating warfarin, assess the INR after the first 2 or 3 doses and at least twice weekly until a stable dose is reached.
  - For long-term treatment, when patient's INR is unstable, unless the dose is substantially outside the therapeutic range, small dosage changes are recommended with repeat INR in 3-4 days.
  - In patients receiving a stable dose of warfarin, the INR should be monitored at least every four weeks.
  - The INR should be measured more frequently when most drugs or herbal medicines are added or withdrawn.
- Many factors affect a patient's response to warfarin and therefore affect the amount of warfarin required by the patient to achieve and/or maintain a therapeutic PT INR. These include other medications, large changes in dietary intake of vitamin K, chronic medical conditions, acute changes in health and physical activity.

Written by Jeff Whissell; reviewed by Michael Mant and Dayle Strachan

Advance Tips

- Dietary vitamin K intake, chiefly from **green leafy vegetables**, should be kept reasonably **constant** from week to week.
- **Concomitant** use of **antiplatelet agents or other anticoagulants** increases the risk of **bleeding**.
- Many drugs and alternative medicinal products potentiate or inhibit the anticoagulant action of warfarin. Thus, the recommendation of increased monitoring frequency with introduction or cessation of most new medications.

- Management of High INR*

INR	Clinical Setting	Therapeutic Options
< 5	No significant bleeding, rapid reversal is not indicated	Reduce warfarin dose, or hold the next warfarin dose
5.0–9.0	No significant bleeding	Hold the next 1-2 doses of warfarin, or omit the next dose of warfarin and administer vitamin K_1-2.5 mg PO
5.0–9.0	Rapid reversal required, e.g. urgent surgery	Vitamin K_1 2-4 mg PO (↓ INR within 24 hours), if INR remains high at 24 hours give additional Vitamin K_1 1-2 mg PO
	No significant bleeding	Hold warfarin and administer Vitamin K1 5-10 mg PO. Use additional Vitamin K_1 if indicated by frequent INR monitoring.
> 9	Serious bleeding	Hold warfarin, administer Vitamin K_1, 10 mg by slow IV infusion. Supplement with fresh plasma, prothrombin complex concentrate or recombinant factor VIIa, depending on urgency.
	Life-threatening bleeding	Hold warfarin therapy and administer prothrombin complex concentrate or recombinant factor VIIa, supplemented with vitamin K_1, 10 mg by slow IV infusion. Monitor INR and repeat as necessary.

***When warfarin is resumed, use lower dose**

"The disgrace of medicine has been that colossal system of self-deception, in obedience to which mines have been emptied of their cankering minerals, the vegetable kingdom robbed of all its noxious growths, the entrails of animals taxed for their impurities, the poison-bags of reptiles drained of their venom, and all the inconceivable abominations thus obtained thrust down the throats of human beings suffering from some fault of organization, nourishment, or vital stimulation."

Oliver Wendell Holmes. Medical Essays by Oliver Wendell Holme, 1987; 265.

ORAL HYPOGLYCEMICS

Biguanides

Drug Class: antidiabetic agents
Drug: **metformin** [Glucophage]

Mechanism of Action & Indications

- **Inhibit gluconeogenesis/hepatic glucose output**, contributing to postprandial glucose lowering. In addition, **increase peripheral insulin uptake and utilization**, decreased fatty acid oxidation.
- Overall effect is improvement in **insulin sensitivity**, leading to decreased fasting and post-prandial blood glucose, and decreased insulin levels.
- For patients with established **type 2 diabetes**, can be used as first line therapy to improve glycemic control, especially in obese patients with insulin resistance syndrome.
- Alternative uses include anti-insulin effect in females with **polycystic ovarian syndrome** and **androgen excess**.

Common Dosages

- Metformin 500-1000mg PO BID with meals. Start at 500mg PO BID, increase by 500mg per week.
- Alternatively, metformin 850mg PO TID.

Adverse Effects & Contraindications

- **Lactic acidosis (wide anion-gap)**:
  - Rare, potentially life-threatening.
  - Physiologic increase in lactate likely related to **enhanced conversion of glucose to lactic acid in intestinal mucosa**.
  - Acidosis can occur with **concomitant severe disease states that promote lactic acid production**.
- **Gastrointestinal**: diarrhea, nausea, anorexia, metallic taste.
- Contraindications to metformin include severe disease states that could precipitate lactic acidosis, including **hypoxia, tissue hypo-perfusion, sepsis, acute renal failure with or without radiographic contrast, hepatic failure**.

Practical Tips

- Monitor for initial **GI intolerance** (especially in the elderly). Greater than 50 % of patients will tolerate maximum dose; 95% will tolerate lower doses.
- Discontinue in patients who are **critically ill**, in **acute renal or hepatic failure**, and in patients **receiving IV radiographic contrast**.
- **Renally excreted** with no intermediary metabolism.
- Compared to sulfonylureas:
  - **No significant hypoglycemia** as monotherapy; effect is anti-hyperglycemic in nature.
  - **Does not promote weight gain**.
  - **Safe** in combination with other classes of oral hypoglycemics, either as first-line or second line combination therapy.
- Can be used in **combination with insulin therapy** (practice varies).

Written by Mike McDonald; reviewed by Laurie Mereu and Cindy Polivchuk

Sulfonylureas

Drug Class: antidiabetic agents
Drugs: **gliclazide** [Diamicron], **glimepiride** [Amaryl], **glyburide** [Diabeta]

Mechanism of Action & Indications

- Stimulates the **release of insulin from pancreatic B cells** both basally and in response to a meal.
- This process involves sulfonylurea binding to the **sulfonylurea receptor** on cell surface, leading to **closure of a voltage gated K^+ channel**. K^+ build-up in that cell resulting in membrane depolarization, and subsequent Ca^{2+} influx. This activates phospholipid protein kinase which triggers the fusion of insulin containing granules to the cell membrane, resulting in the release of insulin.
- Used as second or third line agents for **type 2 diabetics** not on insulin.

Common Dosages

- Gliclazide 80-160mg PO BID, starting with 40-80mg daily
- Gliclazide modified release (MR) 30-120mg PO daily
- Glimepiride 1-8mg PO daily
- Glyburide 2.5-20mg PO BID, starting with 5mg daily

Adverse Effects

- The most common side effect is **hypoglycemia** (particularly with the longer acting sulfonylureas).
- Complications include **rash** (rare, but raises possibility of sulfa allergy), **SIADH** (rarely with chlorpropramide), and **abnormal LFTs** (rare).
- **Sulfonylurea monotherapy**, relative to metformin, is associated with an **increased cardiovascular risk**. Thus, sulfonylurea should not be used as first line agent.
- Associated with an **increase in body mass index**.
- Absolute CONTRAINDICATIONS include **pregnancy**, **allergy to sulfa** or sulfonylurea, **renal and hepatic failure** (delayed drug excretion), **frequent hypoglycemia or hypoglycemia unawareness**, gastroparesis, poor oral intake, type 1 diabetes, altered level of consciousness, severe stress or illness, and perioperatively.
- Use caution in elderly persons who have high risk of adverse events developing from **hypoglycemia**.

Practical Tips

- Given with meals at same time each day.
- Sulfonylureas are excreted renally, so **increased hypoglycemia with renal insufficiency**.
  - Glyburide is not recommended for creatinine clearance <50ml/min.
  - For gliclazide, no dose adjustments probably necessary for renal failure; however, the half life can be prolonged.
  - For glimepiride, starting dose should be 1mg if creatinine clearance <22ml/min.
- Glyburide and glimepiride have particularly long half lives and can be given once daily. These same drugs also **suppress liver glucose output to a greater degree** which can increase the risk of **hypoglycemia**.
- Because of their effect in closing ATP dependent potassium channels, they can **potentially mask ST segment elevation** in acute myocardial infarction. They can also reduce left ventricular ejection fraction during exercise stress testing.
- The **shorter duration sulfonylureas** have a lower risk of hypoglycemia, so they should be used **preferentially** in **elderly patients**.
- **Fluoroquinolones** used in the presence of sulfonylureas may increase the risk of **hypoglycemia.**
- Combined use of **ethanol and glyburide** may cause **disulfiram reactions** and **hypoglycemia**.

Written by Curtiss Boyington; reviewed by Laurie Mereu and Cindy Polivchuk

Thiazolidinediones

Drug Class: antidiabetic agents
Drugs: **pioglitazone** [Actos], **rosiglitazone** [Avandia]

Mechanism of Action & Indications

- Increases **adipose and muscle insulin sensitivity** by increasing glucose utilization and decreasing glucose production.
- Act as ligands for the **peroxisome proliferator-activated receptor gamma (PPAR-γ)** expressed in adipocytes which are **nuclear receptors** that regulate genes involved in carbohydrate and lipid metabolism.
- In patients with impaired glucose tolerance, they **increase insulin secretion** in response to glucose. Drug action is dependent on presence of insulin.
- In animal studies, have been shown to **improve and preserve pancreatic β-cell function**.
- Used for glycemic control in **type 2 diabetics**.

Common Dosages

- Pioglitazone 15-45mg PO daily
- Rosiglitazone 4-8mg PO daily

Adverse Effects & Contraindications

- **Hepatotoxicity** is reported as a rare but proven side effect of both rosiglitazone and pioglitazone.
- **Weight gain** that is both dose and time dependent and results from proliferation of adipocytes and redistribution of fat stores (more peripheral fat).
- **Fluid retention** or edema is common and partly accounts for the weight gain observed and can precipitate or worsen heart failure. **Peripheral edema** is often more severe when combined with another glucose-lowering agent such as insulin.
- **Angioedema** has been reported to be a side effect of rosiglitazone.
- May **initiate ovulation** in premenopausal anovulatory women, increasing the risk of pregnancy.
- **Anemia** has been reported and is thought to be a result of hemodilution from sodium and water retention.
- Rosiglitazone can cause or worsen **macular edema**. Thus, use with caution in patients with macular edema or diabetic retinopathy.
- **Pulmonary edema and congestive heart failure** has been reported in 1-3% of patients and can occur in those with normal systolic function.
- Greater than 10% risk of developing **increased total cholesterol and HDL**. In at least one study **pioglitazone** was shown to **decrease LDL** whereas **rosiglitazone** was more likely to **increase LDL levels**.
- This class of drugs is **CONTRAINDICATED** in patients with **Class II to IV heart failure**, hepatic dysfunction.
- Should **not** be taken with **alcohol** as may cause hypoglycemia.
- Should **not be taken during pregnancy** as effects of drug on pregnancy and while nursing are not known.

Practical Tips

- **Low starting dose** should be used in patients with one or more risk factors for heart failure.
- **Hemoglobin A1c and ALT** should be measured prior to initiation of therapy and then every 2 months for the first year and periodically thereafter. Expect ~1-1.6% absolute decrease in HgbA1c with use of a thiazolidinedione.
- Because the mechanism of action involves gene regulation, onset of action is delayed and glucose control may take **several weeks**.

Written by Samuel Asfaha; reviewed by Laurie Mereu and Cindy Polivchuk

HORMONES

Insulin

Drug Class: insulin

Drugs:

- **Rapid acting—Aspart** [Novorapid], **Lispro** [Humalog]
- **Fast acting—Novolin Toronto**, **Humulin Regular**
- **Intermediate acting—Novolin NPH**, **Humulin N**, **Humulin Lente**
- **Long acting—Humulin Ultralente**
- **Extended long-acting—Glargine** [Lantus]

Mechanism of Action & Indications

- Peptide hormone that binds to insulin receptor on cell surface, resulting in **utilization and storage of glucose.** Glycolysis and glycogen synthesis are stimulated, and gluconeogenesis and glycogenolysis are inhibited. Insulin is given to all type 1 diabetic patients, and many type 2 diabetics.
- Increases **fat storage in adipose tissue** by stimulation of lipoprotein lipase, as well as inhibition of lipolysis and fatty acid synthesis from glucose.
- Promotes amino acid and **protein synthesis in liver and muscles**.
- Stimulates uptake of potassium into cells within 20-30 minutes of administration. Thus, may be used to treat **hyperkalemia** acutely (unlabeled use).

Common Dosages

- Dosages highly individualized. See Practice Tips below for principles of prescribing insulin.

Adverse Effects

- **Hypoglycemia** is the major side effect. In patients with highly labile blood glucose levels, insulin regimen should be adjusted to avoid hypoglycemia, even at the cost of occasional hyperglycemia.
  - Treat **mild to moderate** hypoglycemia (blood sugar <4mmol/L) with **15 grams of carbohydrate** (5 dextrosol 2.75g tablets, 3 packages or 3 teaspoonsful of table sugar dissolved in water, ¾ cup of juice/regular soft drink, or 6 lifesavers or 1 tablespoon of honey). Glucose is the preferred treatment of hypoglycemia due to its rapid absorption in the digestive system. Retest blood sugar in 15 minutes.
  - Treat **severe** hypoglycemia reactions (unconscious patient) with **glucagon 0.5-1mg** IM/IV/SC, repeat in 20 minutes if necessary.
- May cause local skin irritation with itching, edema, pain, and **atrophy or hypertrophy of subcutaneous fat tissue**. Rotation of injection sites is recommended.

Practical Tips on Starting a Patient on Insulin

- For a new patient, the general dose is **0.5units/kg/day** SC in divided dosages.
- For DKA, the general starting dose is **0.1 units/kg IV push**, and **0.1 units/kg/hr IV**.
- All type 1 diabetic patients should be encouraged to be on **multiple daily injections** to achieve good control:
  - 20% of total insulin should be given before each meal.
  - 40% of total insulin dose should be given as basal insulin at bedtime.

Written by David Hui; reviewed by Laurie Mereu and Cindy Polivchuk

- If a patient is unable to do multiple daily injections, consider the **two-thirds, one third rule**:
  - Establishes a baseline for insulin administration using the two main insulins—intermediate-acting and fast-acting. AM dose (given before breakfast) = 2/3 of total daily insulin (2/3=N, 1/3=R), PM dose (given before supper) = 1/3 of total daily insulin (2/3=N, 1/3=R).
- Patients with type 2 diabetes who are on maximum oral antihyperglycemic agents may be started on **bedtime insulin** at 0.1 units/kg to improve control.
- Understanding the pharmacokinetics of different insulin types is essential for fine adjustments of insulin regimen. Blood sugar is checked **4 times/day, before meals and at bedtime**.
- Insulin is **renally excreted**, thus its dose must be reduced in patients with renal failure.
- Consider the use of **metformin** in conjunction with insulin in type 2 diabetics to increase insulin sensitivity and decrease insulin requirements.
- Avoid using **thiazolidinediones** (e.g. rosiglitazone) in combination with insulin as both medications promote **fluid retention**.
- Non-selective β-blockers may mask signs and symptoms of hypoglycemia. Consider use of cardioselective β-blocker agents in diabetics.
- Duration of Action of Insulins and Insulin Analogues

Insulin type/action	Trade names
Rapid-acting analogue (clear)	
Onset: 10-15 min	Humalog (insulin lispro)
Peak: 60-90 min	NovoRapid (insulin aspart)
Duration: 4-5 h	
Fast-acting (clear)	
Onset: 0.5-1 h	Humulin-R
Peak: 2-4 h	Novolin Toronto
Duration: 5-8 h	
Intermediate-acting (cloudy)	
Onset: 1-3 h	Humulin-L
Peak: 5-8 h	Humulin-N
Duration: up to 18 h	Novolin NPH
Long-acting (cloudy)	
Onset: 3-4 h	Humulin-U
Peak: 8-15 h	
Duration: 22-26 h	
Extended long-acting analogue	
Onset: 90 min	Lantus (insulin glargine)
Duration: 24 h	
Premixed (cloudy)	
A single vial or cartridge contains a fixed ratio of insulin (% rapid- or fast-acting to % intermediate-acting insulin)	Humalog Mix25 Humulin (20/80, 30/70) Novolin (10/90, 20/80, 30/70, 40/60, 50/50)

Table adapted from the Canadian Diabetes Association Guidelines 2003

"Remember how much you do not know. Do not pour strange medicines into your patients."

Thayer, WS. Osler the Teacher, in Olser and other papers, 3.

Written by David Hui; reviewed by Laurie Mereu and Cindy Polivchuk

Corticosteroids

Drug Class: anti-inflammatory and anti-proliferative agents

Drugs: **betamethasone**, **cortisone acetate**, **dexamethasone** [Decadron], **fludrocortisone** [Florinef], **hydrocortisone** [Solucortef], **methylprednisolone** [Solumedrol], **prednisolone**, **prednisone**

Mechanism of Action & Indications

- Diffuses through cell membrane to interact with steroid receptors in the cytoplasm, which then enters the nucleus to alter **transcription** of various genes responsible for stress response. It usually takes **hours to days** for maximal effect.
- Overall **catabolic effect** promoting protein and lipid breakdown, and inhibiting protein synthesis in **muscle**, **connective tissue**, **adipose tissue**, and **lymphoid cells**.
- **Anti-inflammatory** and **immuno-modulatory effects** particularly useful in various inflammatory disease states (overwhelming infections, rheumatologic diseases, malignancies). Also used for **physiologic replacement** in adrenal insufficiency.

Common Dosages

- Dosages highly individualized. See Practice Tips below for some principles of prescribing steroids.

Adverse Effects

- Glucocorticoids are associated with **euphoria**, but prolonged use may lead to irritability, **depression**, **psychosis**, memory/concentration loss and decreased libido. Also increases appetite and may contribute to **weight gain**.
- Predisposes to development of **cataracts** and **glaucoma**. Thus, patients on prolonged therapy should be examined by an ophthalmologist regularly.
- May cause **hypertension** although mechanism not well understood. At high concentrations, may promote **sodium and water retention** and may cause hypokalemia via its mineralocorticoid activity.
- Independently increases the risk of **gastritis, ulcer formation, and GI bleeding**. Avoid combined use with NSAIDs which could further increase this risk.
- Hematologic effects include **leukocytosis** through decreased movement of neutrophils out of the vascular compartment. Glucocorticoids also **suppress the inflammatory and immune responses** by stabilizing lysosomes and inhibiting phagocytosis.
- **Elevates blood glucose level** and promotes **insulin resistance** via activation of hepatic gluconeogenesis and limiting peripheral glucose utilization. Blood glucose monitoring may be needed.
- Endocrine side effects include inhibition of responsiveness of the pituitary to GnRH, which results in **decreased gonadotropins and gonadal steroids**. Also may inhibit TSH secretion.
- Promotes **osteoporosis** by inhibiting osteoblast function, increasing bone resorption, enhancing PTH action on bone, decreasing calcium absorption from the gut, and increasing urinary calcium excretion. In addition, **osteonecrosis (avascular necrosis)** of the femoral heads, knees, shoulders, and other bones may occur at supra-physiologic doses.
- Long term use of glucocorticoids in the **supra-physiologic range (>7.5mg/d of prednisone)** could lead to development of **Cushing's syndrome**. The overall catabolic effect contributes to thinning of skin, easy bruising, acne, and **poor wound healing**.
- May increase risk of **cleft palate** if used in pregnancy, although no evidence for development of adrenal insufficiency in offspring.

Practical Tips

- Corticosteroid Equivalent Dosing Table

Corticosteroid	Biological half-life (hours)	Equivalent anti-inflammatory dose (mg)	Relative mineralocorticoid potency
Glucocorticoids			
Short-acting			
Cortisone acetate	8-12	25	2
Hydrocortisone (solucortef)	8-12	20	2
Intermediate-acting			
Methylprednisolone (solumedrol)	18-36	4	0
Prednisolone	18-36	5	1
Prednisone	18-36	5	1
Triamcinolone	18-36	4	0
Long-acting			
Betamethasone	36-54	0.6	0
Dexamethasone (decadron)	36-54	0.75	0
Mineralocorticoid			
Fludrocortisone (florinef)	12-24	10	125

Table adapted and modified from CPS 2005

- Corticosteroid toxicity is related to both the **dose** and **cumulative duration** of exposure. In general, administration of high dose steroid over a few days is safe, while corticosteroid use **over 3 weeks**, especially in the **supra-physiologic range** (>7.5mg/d of prednisone), could lead to various complications.
- Due to **suppression of hypothalamic-pituitary-adrenal axis** by negative feedback loop, it is important to **taper steroid slowly** for any patients on glucocorticoids for >3weeks.
- In association with HPA axis suppression, **stress dose** is required if patient has taken potentially suppressive dose of glucocorticoids for >3 weeks during the preceding year. Prescribe **2x glucocorticoid replacement** (prednisone 15mg/d) during minor stress, and consider **hydrocortisone 300mg/d** in divided doses intravenously during major stress.
- Careful monitoring, patient education, and appropriate **preventive therapy** (calcium, vitamin D, bisphosphonates, proton pump inhibitors) are essential for patients on chronic steroids.
- All patients on chronic steroids should obtain a **medical alert bracelet**.

"One of the first duties of the physician is to educate the masses not to take medicines."

Bean WB. Sir William Osler: Aphorisms, 105.

Topical Corticosteroids

Drug Class: topical anti-inflammatory and anti-proliferative agents

Drugs:

- The **potency** of topical corticosteroids is most commonly classified according to the **vasoconstrictor assay**, based on the degree to which an agent causes cutaneous vasoconstriction on normal human subjects. They range from class one (superpotent) to class seven (least potent). The potency of the class one agent clobetasol propionate (0.05% cream or ointment) is over 1,800 times that of the class seven agent hydrocortisone (1% cream). Because of enhanced penetration, ointments are generally more potent than creams.
- Selected examples of topical corticosteroids in each class:
  - **Class one (super potent)—clobatasol propionate cream or ointment 0.05%**, optimized vehicle (Temovate)
  - **Class two (potent)—amcinonide ointment 0.1%** [Cyclocort]
  - **Class three (potent)—halcinonide ointment 0.1%** [Halog]
  - **Class four (mid-strength)—halcinonide cream 0.025%** [Halog]
  - **Class five (mid-strength)—hydrocortisone valerate cream 0.2%** [Westcort]
  - **Class six (mild)—desonide cream 0.05%** [Tridesilon]
  - **Class seven (least potent)—hydrocortisone 1% cream** [Hytone, others]

Mechanism of Action & Indications

- Corticosteroid diffuses into target cell and binds to the glucocorticoid receptor, which when activated, traverses the nuclear envelop and binds to acceptor sites on DNA, leading to gene regulation and transcription of various mRNA.
- Topical corticosteroids are effective in many **inflammatory** and **proliferative** skin diseases, including **atopic dermatitis**, **psoriasis**, **seborrheic dermatitis**, **contact dermatitis**, and **nummular eczema**.

Common Dosages

- Mainly for ease of application, patients are often empirically instructed to apply topical corticosteroids **sparingly twice daily**. There are little clinical data to determine optimal frequency of application. One study showed that six applications daily were not more effective than three applications daily for corticosteroid responsive dermatoses.
- With chronic use, topical corticosteroids (especially the potent agents) show **decreased efficacy**, a phenomenon known as "**tachyphylaxis**".

Adverse Effects

- **Localized atrophy**, **striae**, **telangiectases**, pigment changes, and hypertrichosis.
- **Worsening of acne**, **peri-oral dermatitis**, and **rosacea**.
- **Masking** of the symptoms of infections such as tinea and scabies.
- Chronic use of potent topical corticosteroids in large areas of the body can induce **hypothalamic-pituitary axis suppression**, especially in infants and children.
- Contact dermatitis to the vehicle, or the corticosteroid molecule.

Practical Tips

- Absorption of topical corticosteroids is highest on **mucous membranes**, followed by the scrotum, eyelid, face, chest, back, arms and legs, dorsa of hands and feet, and palms and soles.
- With few exceptions, only the **least potent corticosteroids should be used on mucosal surfaces and the face**.

Written by Andrew Lin

Levothyroxine

Drug Class: thyroid hormone replacement
Drug: **levothyroxine** [Eltroxin, Synthroid]

Mechanism of Action & Indications

- **Thyroxine (T4)** is normally produced by the **thyroid gland**, which is then converted to **triiodothyronine (T3)**, the more biologically **active** form, by deiodination at various tissues (esp. liver and kidney). T3 then acts by **modifying gene transcription** in virtually all tissues to **alter rates of protein synthesis** and substrate turnover.
- Used in replacement therapy in **hypothyroidism**, and in situations when thyrotropin (TSH) **suppression** is indicated, such as thyroid carcinoma.

Common Dosages

- For hypothyroidism, levothyroxine 1.6mcg/kg PO daily (usual maintenance dose 50-200mcg/day)

Adverse Effects & Contraindications

- Physiologic hormone and thus **rarely any side effects** if used in therapeutic range.
- In the supratherapeutic range, may produce symptoms of hyperthyroidism. Rare but serious side effects include **angina**, **arrhythmias**, **myocardial infarction**, and **seizures**.

Practical Tips

- Symptoms of **hypothyroidism** may occur if the dose is too low.
- For **elderly** or **patients with cardiac disease**, consider starting levothyroxine at **quarter to half of regular dose** and titrate slowly. Monitor for tachycardia and angina.
- Titrate dose every **six to eight weeks** until TSH within normal range. Three to four months after the start of treatment, measure the serum free or total T4 as well to decide any need for a minor adjustment in the dose. Once target dose reached, may check **TSH annually**.
- Available in PO and IV formulations. **Intravenous** form is a lot more **expensive**, and should be reserved for patients who are in **myxedema coma**, or **cannot take PO medications for more than 5-7 days** (e.g. post complicated GI surgery).
- The half life of thyroxine is **six days**. Thus, thyroxine **can be held for a few days without effect**. Serum concentrations usually fall to the hypothyroid range within two weeks after therapy has been stopped.
- T3 is not used to diagnose hypothyroidism because it may be transiently decreased by non-thyroid illness or malnutrition.
- Absorption of levothyroxine may be **decreased by iron salts**. Separate administration as much as possible.
- For TSH suppression in well differentiated **thyroid cancer**, levothyroxine doses are highly individualized. In general, **>2mcg/kg/day** may be needed to suppress TSH (<0.1mU/L).
- In **pregnancy**, dosage may need to be **increased** to maintain TSH in desired range. Chest **TSH** each trimester and 4-6 weeks after any dose adjustments.

"Treatment is to be always directed to the part which is mostly in trouble."

Celsus, Aulus Aurelius Cornelius. De Medicina, book I, ch. 30. 1938, p. 57.

Written by David Hui; reviewed by Laurie Mereu and Cindy Polivchuk

BONES & MINERALS

Bisphosphonates

Drugs: **alendronate** [Fosamax], **clodronate** [Bonefos], **etidronate** [Didronel, Didrocal], **pamidronate** [Aredia], **risedronate** [Actonel], **zoledronate** [Zometa]

Mechanism of Action & Indications

- **Inhibits bone resorption** via action on osteoclasts or their precursors
- Oral bisphosphonates such as **alendronate**, **etidronate, and risedronate** are used in the **prevention** and **treatment** of **osteoporosis**, as well as treatment of **Paget's disease**.
- Intravenous **pamidronate** and **clodronate** are used to treat life-threatening **hypercalcemia**.

Common Dosages

- For treatment of osteoporosis, etidronate 400mg daily ×14 days and 500mg of elemental $CaCO_3$ ×76 days (Didrocal kit is a 3 month cycle)
- For treatment of osteoporosis, alendronate 70mg PO weekly or 10mg PO daily
- For treatment of osteoporosis, risedronate 35mg PO weekly or 5mg PO daily
- For treatment of hypercalcemia, clodronate 1500mg in 500cc normal saline SC/IV over 4-6 hours
- For treatment of hypercalcemia, pamidronate 60-90mg in 500ml normal saline IV over 4-6 hours

Adverse Effects

- Oral bisphosphonates
  - May cause significant **gastrointestinal** symptoms, including esophagitis, esophageal ulcers, and even rarely esophageal stricture.
  - **Dyspepsia** is common.
- Intravenous bisphosphonates
  - **Severe local phlebitis** will occur if given in rapid or concentrated infusion.
  - Can induce a **transient flu-like febrile illness** lasting 24 hours, with no significant long term consequences.
  - Use the **smallest effective dose**, as over dosage can lead to hypocalcaemia.
  - Must NEVER be given in an IV bolus, always dilute and give by **slow IV infusion**.
  - According to case reports, bisphosphonates may predispose patients to **osteonecrosis of the jaw** (especially zoledronic acid). Risk factors include diagnosis of cancer, concomitant therapies (chemotherapy, radiation, corticosteroids), and comorbid conditions (e.g. anemia, coagulopathies, infection, preexisting oral disease). If patients develop a dental infection while on bisphosphonates, consider withdrawal of the bisphosphonate until infection is resolved; if patient is high risk, treat dental infections before initiation of bisphosphonate therapy.

Practical Tips

- As poorly absorbed orally, oral bisphosphonates must be **administered at least 30 minutes before food**, **drink** (except water), or other **medications**.
- Patient must remain **upright for at least 30 minutes after administration**.
- As bisphosphonates cause hypocalcemia, patients receiving an oral bisphosphonate should also receive **1000 mg of elemental calcium** and **800 IU of vitamin D daily**.
- When treating hypercalcemia with intravenous bisphosphonates, do not repeat the dose until **optimal effect** is seen (in approximately **48 hours**); **effect peaks at 7 days** and **persists for 2-3 weeks** in hypercalcemia of malignancy.

Written by Peter Hamilton; reviewed by Laurie Mereu and Melissa Dutchak

Calcium

Drug Class: electrolyte supplement

Drugs: **calcium carbonate** [Tums, Caltrate], **calcium citrate**, **calcium gluconate**, **calcium chloride**

Mechanism of Action and Indications

- Oral calcium is absorbed by active transport in the **duodenum** and passively throughout the small bowel.
- **1,25 dihydroxyvitamin D** influences the rate-limiting step of calcium absorption in the gut.
- Calcium and phosphate homeostasis is regulated by the hormone **PTH**.
- Indications
  - Treatment and prevention of **hypocalcemia**, **hypoparathyroidism**, **chronic hyperphosphatemia**, and **osteoporosis**.
  - Heartburn symptom-relief as an **antacid**.
  - Phosphate binder in **renal dysfunction**. Binds to dietary phosphate to form insoluble calcium phosphate which is excreted in feces.
  - Treatment of **hypocalcemic tetany** and **hyperkalemia**.

Common Dosages

- Doses are highly dependent on indication and type of calcium preparation.
- Calcium carbonate 500-1000mg (200-400mg elemental calcium) PO BID–QID with meals for treatment and prevention of osteoporosis and as a phosphate binder.
- Calcium gluconate 10 cc of 10% solution (90 mg elemental calcium) IV slow push for life-threatening hyperkalemia (usually K>6.5mmol/L or ECG changes).

Adverse Effects & Contraindications

- Common GI side effects include **constipation**, **dyspepsia**, **nausea**, **vomiting**, **diarrhea**, flatulence, and metallic taste.
- Common metabolic side effects include **hypercalciuria**, **hypercalcemia**, **hypomagnesemia**, and **hypophosphatemia**.
- Milk-alkali syndrome may occur in very high chronic dosing.
- Rare but serious adverse effects with parenteral calcium include arrhythmias such as **bradycardia** and **ventricular fibrillation**, **hypotension**, and **tissue necrosis**.
- Contraindications include **hypercalcemia**, **hypophosphatemia**, **digitalis toxicity**, **ventricular fibrillation**, and **hypercoagulability**.

Practical Tips

- Vitamin D must be present in order for intestinal absorption of calcium to occur.
- Recommended daily intake of elemental calcium from all sources:
  - Men and Women age 19-50: 1000mg daily.
  - Men and Women age 50+: 1500mg daily.
  - Pregnant/lactating women: 1000mg daily.
- Calcium supplementation over 500mg/day should be given in **divided doses** for optimal absorption.
- Oral calcium absorption is impaired in **achlorhydria**. **Administer with food** or use calcium citrate.
- Calcium **reduces the absorption** of tetracycline, atenolol, iron, quinolones, alendronate and zinc absorption. Space out administration times for better absorption.
- **Calcium channel blocker** effects may be **diminished** when taking calcium.
- Hypercalcemia may result with **concurrent thiazide diuretics** and **calcium use**.
- Corrected calcium [mmol/L]=0.02×(40 – serum albumen [g/L]) + measured calcium [mmol/L].

Written by Winnie Leung; reviewed by Peter Hamilton

Vitamin D

Drug Class: fat soluble vitamin

Drugs: **vitamin D3**, **vitamin D2** [Drisdol, Ostoforte], **calcitriol** [Rocaltrol], **alfacalcidiol** [One-alpha]

Mechanism of Action & Indications

- Vitamin D3 **(cholecalciferol)** is synthesized in the skin from 7-dehydocholesterol during exposure to ultraviolet light. This and dietary vitamin D are then converted by 25 hydroxylase in the liver to 25(OH)-vitamin D_3 **(calcidiol)**, and subsequently converted by 1α hydroxylase in the kidney to the most active form 1,25$(OH)_2$-vitaminD_3 **(calcitriol)**.
- Promotes the absorption of calcium in the gut and retention at the kidneys. This **increases serum calcium levels**, and **decreases phosphate levels**, **PTH** and **bone resorption**.
- Indicated for treatment of **osteoporosis** and **hypoparathyroidism**.

Common Dosages

- Vitamin D3 400-800 units PO daily for osteoporosis
- Vitamin D2 5mcg (200 units) PO daily for dietary supplementation
- Vitamin D2 0.625-5mg (25,000–200,000 units) PO daily for hypoparathyroidism
- Calcitriol 0.25mcg PO daily to BID

Adverse Effects & Contraindications

- Generally well tolerated, may cause nausea, vomiting, headache, metallic taste.
- Serious adverse effects (frequency not defined) include arrhythmia, hypertension, psychosis, mild acidosis, pancreatitis, vascular/nephrocalcinosis (rare), azotemia.
- Contraindications include **hypercalcemia**, symptoms of **vitamin D toxicity** (hypercalcemia, weakness, fatigue, lethargy, anorexia), and **malabsorption syndromes** (may require fat-soluble vitamin analogue such as calcifediol).
- The toxic dose of vitamin D is unclear, but is above 2000 units per day.

Practical Tips

- **Vitamin D3 shows greater potency** than Vitamin D2, therefore it is more commonly prescribed.
- **Vitamin D** stimulates calcium absorption, thus it is usually **given in conjunction with calcium supplementation**. It is unclear whether vitamin D benefits patients who are not receiving calcium supplementation.
- Recommended daily intake of vitamin D3 from all sources:
  - Men and Women age 19-50: 400 units (10 mcg) daily.
  - Men and Women age 50+: 800 units (20 mcg) daily.
  - Pregnant/lactating women: 400 units daily.
- In temperate areas, cutaneous production of vitamin D virtually ceases in the winter.
- With calcitriol, it is recommended that **serum calcium and creatinine**, and **urinary calcium** be measured routinely. Calcium dose should be lowered if hypercalciuria, azotemia, or hypercalcemia develops.
- Alfacalcidiol (1α(OH)-vitamin D3) is interchangeable with calcitriol for treatment of secondary hyperparathyroidism in renal disease as long as liver function is normal.

Written by Winnie Leung; reviewed by Alan McMahon

FLUIDS & SUPPLEMENTS

Intravenous Fluids

Introduction

- Crystalloids and colloids
  - **Resuscitation fluids** can be either **crystalloids** or **colloids**, whereas **maintenance fluids** are **crystalloids** only. Normal saline and Ringers are crystalloids. Blood, plasma, pentaspan and albumin are colloids.
  - Crystalloids are **cheaper, easily accessible** and **safer**.
  - Colloids allow for **faster resuscitation** per unit of volume given, are **more expensive** and it may take longer to get them to the bedside.
  - Patient mortality and morbidity depends on **fast** restoration of intravascular volume to ensure **end organ perfusion**.
- Isotonic and hypotonic solutions
  - **Isotonic solutions** have tonicity similar to plasma and are used for **volume expansion**. These include **normal saline (0.9%)** and **Ringers Lactate**.
  - **Hypotonic solutions** deliver some free water and are generally not used for volume expansion as they can lead to hyponatremia. They are used for **maintenance fluid** in NPO patients and to **correct hyperosmolar states** (e.g. hyperglycemia or hypernatremia with volume depletion). Hypotonic solutions include dextrose water (**D5W** or **D10W**), **half normal saline** (0.45%) and **$^{2}/_{3}$D5W$^{1}/_{3}$NS**.
  - **Daily requirements** for an adult are 2000 to 2500ml (20 to 40ml/kg/day) of water, 50 to 100mmol of sodium, and 20 to 60 mmol of potassium.
  - **Additional** fluid and electrolytes will be needed for insensible losses associated with **fever**, **diarrhea**, **vomiting**, **NG suction**.
- To prevent hypokalemia, ALWAYS ask if you need to **supplement the potassium** especially when using **large intravenous volumes**, **diuretics** or the patient is **NPO**.
- The composition of commonly used fluids is shown in the following table. Further details on specific solutions are discussed below.

Resuscitation fluids	pH	Na^+ mM	K^+ mM	Cl^- mM	Ca^{2+} mM	Lactate mM	Glucose	Osmol mM
NS 0.9 %	5.0	150	0	150	0	0	0	308
Ringer's	6.5	130	4	109	3	28	0	275
Pentaspan (Pentastarch 100g/L)	5.0	154	0	154	0	0		326
Albumin 5% (Albumin 50 g/L)	6.4-7.4	130-160	<1	130-160	0	0	0	309
Albumin 25% (Albumin 250 g/L)	6.4-7.4	130-160	<1	130-160	0	0	0	312
Maintenance fluids	**pH**	**Na^+ mM**	**K^+ mM**	**Cl^- mM**	**Ca^{2+} mM**	**Lactate mM**	**Glucose**	**Osmol mM**
$^{1}/_{2}$NS	5.0	77	0	77	0	0	0	154
D5$^{1}/_{2}$NS	4.5	77	0	77	0	0	50g/L	406
$^{1}/_{3}$NS$^{2}/_{3}$D5W	4.2	51	0	51	0	0	33g/L	269
D5W	4.0	0	0	0	0	0	50g/L	252
D10W	4.0	0	0	0	0	0	100g/L	504

Written by Martina Puchyr; reviewed by Peter Hamilton and Catherine Sych

Hypertonic Saline 3%

- Use with extreme caution as rapid shifts in plasma sodium can lead to **osmotic demyelination syndrome** also known as central pontine and extrapontine myelinolysis.
- Used to treat **acute symptomatic hyponatremia** (Na<115meq/L).
- Do **NOT** correct faster than **8mmol/L per day** at a rate of no more than **0.5 to 1meq/L per hour**. If the patient is malnourished, hypokalemic or alcoholic do not correct faster than 4mmmol/L per day
- Administer no faster than **50 to 100ml of 3% saline over one hour**. Calculate the dose and rate of administration for Na replacement using the on line Hypertonic and Normal Saline Infusion Calculator (www.globalrph.com/hypertonicsaline.cgi) and monitor electrolytes frequently.
- Do **NOT** attempt to **completely** correct the sodium level using 3% saline. Aim for a sodium of **120 to 125mmol/L** or an increase of **6 to 8 mmol/L**, then switch to an alternative therapy.
- **NEVER** administer without **discussion** with the senior resident or attending physician.
- Patients with **seizures** due to hyponatremia must be referred to **ICU**.

0.9% Normal Saline (NS)

- To expand **intravascular volume** by one liter one must give 4 liters of NS.
- Excessive resuscitation with NS will result in **non-anion gap hyperchloremic metabolic acidosis** as well as **hypernatremia**. Large volumes will also result in **dilution** of RBCs, platelets and coagulation factors.

Ringer's Lactate (RL)

- Has same intravascular expansion properties as normal saline.
- **Lactate** is converted to **bicarbonate** by the liver. In **liver failure** and **lactic acidosis**, lactate is not efficiently metabolized and Ringer's lactate **may worsen lactic acidosis**.
- The solution also has 4 mmol/L of potassium. In patients with **renal insufficiency** it may contribute to **hyperkalemia**.
- Lower sodium concentration in Ringer's lactate reduces the risk of hypernatremia when compared to normal saline.

Pentaspan

- Hydroxylated starch that should not exceed maximum infusion of **1.5L/24 hours**. **One litre of pentastarch** will expand volume by **1-2 litres**.
- Before administration ensure Pentaspan solution is clear. In addition to risk of septic infusions, may also cause **hypersensitivity** and **anaphylaxis**.
- Associated with **coagulation abnormalities** and **hemorrhage**. It may also precipitate **volume overload** in patients with CHF.
- CONTRAINDICATIONS include **sensitivity reaction** to hydroxylated starch. Patients with **renal insufficiency** may not be able to renally excrete pentaspan, further precipitating renal failure. Do NOT use in **pregnancy**.

Albumin

- **5% albumin** is **oncotically equivalent** volume for volume to human plasma.
- **25% albumin** is **hyperoncotic** relative to human plasma, and will **expand intravascular volume four to five fold** by drawing fluid from interstitial space.
- Albumin infusion can be used as an **adjunct** in the treatment of **hepatorenal syndrome**.
- Post paracentesis albumin infusion might not be necessary for a single paracentesis of **less than 4L**. For large volume paracentesis, albumin infusion should be considered.
- There is convincing evidence that the infusion of albumin in **critically ill patients** is associated with **increased mortality**. As a consequence albumin infusion should NOT be used as a volume expander in these circumstances (Cochrane review).
- It is **NOT** to be used for **nutritional support**.

- A blood product and thus associated with risk of transfusion such as **infections** and **allergic reactions**.
- To **prevent hemolysis**, all albumin solutions contain physiologic amounts of **sodium** (130 to 160mmol/L).
- In general should not be infused faster than **1 to 2ml per min**.

Magnesium Sulphate

- Magnesium deficiency is seen in **malnutrition**, **alcoholism**, **malabsorption**, **chronic diarrhea**, and **drugs** including amphotericin B, cisplatin, cyclosporine and aminoglycoside.
- Hypomagnesemia can cause **delirium**, **tetany**, **ataxia**, **nystagmus** and **seizures**. It prolongs the **PR and QT intervals**, and may lead to **torsade de pointe**.
- Hypomagnesemia may also be associated with **hypokalemia** and **hypocalcemia**.
- Urine magnesium greater than **1mmol/day** in the presence of hypomagnesemia indicates renal loss.
- Administration of magnesium sulphate
  - Mild: **oral supplement** (e.g. milk of magnesia 15ml PO QID). Limiting factor is diarrhea. Magnesium glucoheptonate 30ml PO daily to BID is an alternative.
  - Severe: **1-2g $MgSO_4$ IV over one hour** followed by **6g in 1L over 24hrs**. Then check serum level.
- Usually given at **1g (4mmol) per hour**, with maximum infusion rate of 2g per hour. During infusion, **hypotension** may develop.
- Contraindications include **heart block**, **renal impairment**, **myocardial damage**, **hepatitis**, and **Addison's disease**.

Potassium Phosphate

- **Mild** asymptomatic **hypophosphatemia** requires NO replacement therapy.
- Symptomatic **severe** hypophosphatemia may require **IV therapy**. **Rapid** IV infusion can lead to **hypotension** and **death**. Infuse over **six hours** and **monitor phosphate**, **potassium** and **calcium** levels.
- A common dose of potassium phosphate is **22mmol IV** over 6 hours, which contains 22mmol of potassium and 15mmol of phosphate.
- CAUTION: hyperphosphatemia can lead to hypocalcaemia, metastatic calcification and renal failure.

Sodium Bicarbonate

- **1 ampule** of sodium bicarbonate contains **50mmol of $NaHCO_3$** in 50ml of water. A bicarbonate drip is usually prepared by adding 3 ampules to **D5W** to make up 1 litre. This resulting solution is almost **isotonic** (150mM). Depending on renal function and serum potassium, one may also add 20 to 40mmol of KCl/L of D5W.
- Used for treatment of **metabolic acidosis** such as **lactic acidosis**, **hepatic failure**, **and ACLS**. Sodium bicarbonate should NOT be used as first line therapy in resuscitation as there is no evidence for its benefit. Also not indicated in diabetic ketoacidosis.
- Do NOT **over treat** an acidosis as this will lead to a **metabolic alkalosis** and result in impaired oxygen delivery, hypokalemia and hypocalcemia.
- Other indications include **hyperkalemia**, **urine alkalinization** in overdoses with weak acids including salicylic acid and tricyclic antidepressants.
- **Oral sodium bicarbonate** can be used to treat **renal tubular acidosis**. Use 600mg tablets at a dose of 1 to 2mmol/kg/day aiming for a serum bicarbonate greater than 22mmol/L.
- **Hypokalemia** and **pulmonary edema** are potential side effects.

Folic Acid

Drug Class: water soluble vitamin
Drug: folic acid

Mechanism of Action & Indications

- Folate plays a key role in **DNA synthesis**, with significant implications for cell growth and production.
- Supplemental daily folic acid should be given to patients with **chronic folic acid deficiency states** (nutritional, alcoholism, malabsorption) and **elevated demand** (hemolytic anemia, pregnancy, exfoliative skin disorders).

Common Dosages

- Folic acid 1-5mg PO daily for most cases.
- Routine supplement in pregnancy is now standard of practice. Women with a neural tube defect in a previous pregnancy should use 5mg daily.

Adverse Effects

- Minimal side effects.
- Toxicity does not occur as it is **water soluble** and **renally excreted**. Vitamin toxicity is more likely to occur with the **fat soluble vitamins** (A, D, K & E).
- Folic acid may **mask vitamin B12 deficiency**. When used alone in combined B12 and folic acid deficiency, it can precipitate **subacute combined degeneration** (see vitamin B12).

Practical Tips

- **Supplementation in pregnancy** will prevent neural tube defects.
- **Phenytoin** and **carbamazepine** can cause **folic acid deficiency**. If necessary supplement with folic acid 1mg daily, especially in pregnancy. On the other hand, folic acid can **increase the metabolism of phenytoin** and levels should be monitored.
- **Chronic methotrexate therapy** can cause folic acid deficiency leading to pancytopenia.
- Severe folic acid deficiency can lead to **pancytopenia**, **glossitis**, **stomatitis** and **weight loss**.
- **Red blood cell folic acid** is a more accurate reflection of deficiency than serum folic acid level especially at MCV >100.
- The **reticulocyte count** should increase within one week of starting therapy.
- **Macrocytosis, anemia and pancytopenia** from folic acid antagonists such as **methotrexate** should be treated with **folinic acid (Leucovorin)** in "rescue".
- Dietary supplementation with vitamin B12 and folate to **lower homocysteine levels** does not provide any cardiovascular benefit, and might be **associated with harm** (HOPE 2 and MORVIT trials).

"I would protest against the usurpation on the part of these men [purveyors of pharmaceutical] of our function as teacher… What right have Z. & Co. to send on a card directions for the treatment of anemia and dyspepsia, about which subjects they know as much as a newborn babe, and if they stick to their legitimate business, about the same opportunity of getting information! For years the profession has been exploited in this way until the evil has become unbearable."

Sir William Osler. The Treatment of Disease. Can Lancet 1909; 42:899-912.

Written by Peter Hamilton; reviewed by Anthony Woods and Gregg Holowaychuk

Kayexalate

Drug Class: potassium binder
Drug: sodium polystyrene sulfonate [Kayexalate]

Mechanism of Action & Indications

- Resin **exchanges** sodium ions for potassium ions (also binds calcium and magnesium to a lesser degree) in the large intestine.
- Used for treatment for **hyperkalemia** (K>6.0mmol/L).

Common Dosages

- Kayexalate 15g (60ml) PO daily-QID x1 day
- Kayexalate 30-50g PR q6h x1 day
- Ensure that orders for monitoring electrolytes are included

Adverse Effects

- Metabolic side effects include **hypernatremia**, hypokalemia, hypocalcemia, and hypomagnesemia.
- Gastrointestinal side effects include intestinal necrosis (rare), intestinal obstruction, anorexia, **constipation/stool impaction**, **nausea and vomiting**.
- Tastes like river water.

Practical Tips

- Onset of action is 1-2 hours. Thus, kayexalate should NOT to be used as the sole management of **LIFE-THREATENING** hyperkalemia (i.e. with ECG changes).
- For life-threatening hyperkalemia:
  - 1 amp (10ml) of 10% calcium gluconate infused over 2-3 minutes, AND
  - 10 units of humulin R IV bolus and 1 amp (50ml) D50W, AND/OR
  - 1 amp of 7.5% sodium bicarbonate, especially if patient also has a metabolic acidosis.
  - Look for **iatrogenic causes** of hyperkalemia and stop any contributing drugs if possible (NSAIDs, ACE Inhibitors, ARBs).
- By exchanging sodium for potassium, kayexalate promotes fluid retention. Thus, consider the use of calcium resonium instead of kayexalate in hyperkalemic patients with **fluid-overloaded states** (e.g. congestive heart failure).
- Volume expansion followed by **loop diuretic (furosemide)** will also increase renal potassium excretion.
- Do NOT prescribe open-ended order. Always have a stop or reassess data as severe **hypokalemia** can occur.

"When [no therapy] avails to ward off the fatal ending, it is still no small portion of [the physician's] art to rid his patient's path of thorns if he cannot make it bloom with roses."

Stille, Alfred. Medical News. 1884; 44:433-38.

Written by Vijay Daniels; reviewed by Alan McMahon and Margaret Ackman

Potassium

Drug Class: electrolyte supplement
Drugs: **potassium** [Apo K, K-10, KCl, K-Dur, Micro K, Slow K]

Mechanism of Action & Indications

- Potassium is a key intracellular cation. It plays a key role in many physiological processes, including transmission of **nerve impulses** in cardiac, skeletal muscle, and brain tissue; **contraction of cardiac, skeletal, and smooth muscles**; maintenance of **normal renal function** and **acid-base balance**, and maintenance of intracellular tonicity.
- Used for prevention or treatment of hypokalemia.

Common Dosages

- Apo-K (oral tablet) 8mEq
- K-10 (oral solution) 10% solution, 20mEq (15ml)
- KCl IV (parenteral) in various IV solutions (e.g. NS, D5W, RL) 10mEq, 20mEq, 40mEq
- K-Dur (oral tablet) 20mEq (1500mg)
- Micro-K (oral tablet) 8mEq
- Slow-K (oral tablet) 8mEq
- Potassium phosphate (parenteral) 22mEq in 250ml D5W (more for PO_4 supplementation)

Adverse Effects & Contraindications

- Gastrointestinal (>10%)—**nausea and vomiting**, **bloating**, **abdominal discomfort**, diarrhea, flatulence.
- Less common (<10%)—**hyperkalemia**, **bradycardia**, **muscle weakness**, dyspnea, vein irritation and local tissue necrosis with extravasation.
- Uncommon (<1%)—**heart block**, **hypotension**, **paralysis**, paresthesias, rash, arrhythmia, abdominal pain, chest pain, ulcerative GI lesions.
- Contraindications include **hyperkalemia**, especially in patients with severe renal impairment, and **severe tissue trauma**.

Practical Tips

- Well absorbed from the upper GI tract. Thus, oral form is as effective as intravenous as long as GI tract intact. As **oral form is safer and as effective** as intravenous potassium, it should be tried first in patients with **low to moderate hypokalemia (>2.5mmol/L)**.
- Oral potassium supplements should be taken with **plenty of fluids**, as gastrointestinal side effects such as nausea, vomiting, and abdominal bloating are common.
- Oral potassium is often **started in conjunction with diuretics** such as furosemide (Lasix), which cause hypokalemia. The usual adult dosing in these cases is 20-40 mEq/day divided into either once daily (QD) or twice daily dosing (BID) regimens.
- Parenteral (IV) formulations of potassium may be added into the patient's maintenance IV fluids, which is preferred over using intermittent KCl boluses. For example, IV NS with 20 mEq KCl/L @ 100ml/hr.
- Intermittent **KCl boluses** should only be used in cases of **severe hypokalemia (<2.5mmol/L)**. For example, IV KCl 10mEq in 100ml D5W over 1 hour (through a peripheral IV line), up to a total of three times. Do not exceed this amount or rate!
- In ICU settings where a central line and monitoring is present, **higher concentration of KCl boluses** (20mEq in 100ml D5W) **infused through central venous lines is possible**, but not recommended due to increased risks of cardiac/arrhythmic toxicities in particular.

Written by Roger Tsang; reviewed by Alan McMahon and Gregg Holowaychuk

- Normal daily requirements for potassium in adults is **40-80mEq/day** or **3500mg** (in children, 2-3 mEq/kg/day). This is achievable with a normal daily dietary intake.
- Symptoms of hypokalemia include **muscle weakness** and **paralysis**. ECG abnormalities in hypokalemia include **T wave flattening**, development of **U wave**.
- Prior to starting potassium supplementation, the **cause of hypokalemia should be elucidated and corrected** if possible. Etiologies include diuretic therapy, vomiting, diarrhea, prolonged parenteral nutrition, diabetic ketoacidosis, and primary or secondary hyperaldosteronism.
- Potential increased **serum potassium levels** when used with **potassium-sparing diuretics** or **ACE inhibitors**.

"All substances are poisonous, there is none which is not a poison; the right dose differentiates a poison from a remedy."

Paracelsus. Four Treatises of Theophratus von Hohenheim called Paracelsus 1941; 22.

Vitamin B12

Drug Class: water soluble vitamin
Drug: **vitamin B12**

Mechanism of Action & Indications

- Vitamin B12 plays a key role in **DNA synthesis**, with significant implications for cell growth and production.
- Used for treatment of **vitamin B12 deficiency** with or without **subacute combined degeneration**.

Common Dosages

- In patients who cannot absorb vitamin B12, give 100μg IV or SC x5d, then monthly.
- In patients without an absorption problem, give 2mg oral daily (equally effective as parenteral route).

Adverse Effects

- As it is water soluble and renally excreted, there are rarely any adverse events.
- With a very brisk reticulocytosis, **hypokalemia** can rarely occur as the potassium is incorporated into the red cell.

Practical Tips

- Consider giving **vitamin B12 injection** when treating **severe folate deficiency** as **use of folate alone** in the presence of vitamin B12 deficiency can rarely lead to neurologic sequelae with **subacute combined degeneration**.
- There is **no evidence** for the benefit of vitamin B12 in chronic fatigue, depression, alcoholism or musculoskeletal injury.
- As it is water soluble and renally excreted, there is **no point in giving larger than prescribed doses**.
- Regarding vitamin B12 deficiency:
  - Always consider this diagnosis in **unexplained dementia**, especially if there are long tract signs and/or peripheral neuropathy.
  - Suspect when the MCV is increased and **hypersegmented neutrophils** on peripheral smear.
  - Dietary deficiency is **rare** except in strict vegans.
  - Absorption from the gut involves the presence of **intrinsic factor** from the **parietal cell** and the presence of a **specific receptor** in the **terminal ileum**.
  - **Subacute combined degeneration** is due to severe vitamin B12 deficiency with involvement of the peripheral nerves along with dorsal column and spinothalamic tracts in the spinal cord. Patients may present with **paresthesia in hands and feet**, **loss of vibration and position sense**, **progressive spastic weakness with ataxia**, as well as **optic atrophy** and **dementia** (megaloblastic madness).

"Polypharmacy is a prosthesis for the physician's incompetence. The less he knows, the more prescriptions he writes."

Zeljko Poljak, Croatian Medical Quotations.

Vitamin K

Drug Class: fat soluble vitamin
Drug: vitamin K

Mechanism of Action & Indications

- Vitamin K refers to a group of three fat-soluble vitamins called the quinones. **Phylloquinone (K1)** occurs in green plants, **menaquinone (K2)** is synthesized by intestinal bacteria, and **menadione (K3)** is manufactured synthetically.
- **Factors II, VII, IX, X, protein C and protein S** are all **vitamin-K dependent**. Vitamin K is also necessary for the synthesis of osteocalcin, an important mediator of calcium deposition into the bone matrix.
- Clinical use included situations when **anti-coagulation must be reversed** such as bleeding, emergent surgery or supra-therapeutic INR (usually >9 or if at risk of acutely bleeding or acutely bleeding).
- Other indications include **vitamin K deficiencies** such as celiac disease, steatorrhea, and bile deficiency (e.g. obstructive jaundice).

Common Dosages

- Vitamin K 5-25mg PO x 1 dose (depending on degree of INR elevation)
- Vitamin K 1-10mg IV x 1 dose (depending on degree of INR elevation)

Adverse Effects & Contraindications

- **Risk of anaphylaxis** with intravenous preparations, therefore run intravenous preparations slowly (over 20-30 minutes).
- Adverse effects are otherwise **rare** and include: abnormal taste, anaphylaxis, cyanosis, diaphoresis, dizziness (rarely), dyspnea, GI upset (oral), hemolysis in neonates and in patients with G6PD deficiency, hypersensitivity reactions, hypotension (rarely), pain, tenderness at injection site, and transient flushing reaction.
- **AVOID IM injections** of vitamin K to reverse anticoagulation – the injection itself may cause significant bleeding. Both IM and SC routes have erratic absorption and can lead to warfarin resistance.

Practical Tips

- If anticoagulation must be reversed quickly, consider using **fresh frozen plasma in addition to Vitamin K**. Fresh frozen plasma works quickly and has a short half-life. It is a blood product and has the risks associated with all blood products.
- Vitamin K is **fat soluble**, and depends on proper gastrointestinal function for absorption. If using vitamin K in situations where patients may have **decreased intestinal absorption** (e.g. decreased bile release), **do not use oral preparations**.
- Onset of action: **quickest with parenteral preparations** (1-2 hours vs. 6-12 hours for oral)
  - If INR is 5-9 use vitamin K only if at increased risk of bleeding (1-5 mg PO).
  - If INR is >9 give vitamin K (3-5 mg) PO.
  - If INR is >20 or there is any serious bleeding give 10mg IV.
- **Large doses (10-15 mg) of vitamin K should be avoided** when reversal of anticoagulation is meant to be temporary. **Coumadin resistance** may last up to a week after discontinuation of vitamin K.
- For patients requiring **elective invasive procedures** who are **on anticoagulant therapy**, may consider switching to **unfractionated heparin** for a period of time (**with or without vitamin K to reverse anticoagulation**).

MISCELLANEOUS

Anti-Histamines

Drugs:

- **First generation—chlorpheniramine** [Chlor-tripolon], **diphenhydramine** [Benadryl]
- **Second generation—cetirizine** [Reactine], **loratadine** [Claritin]

Mechanism of Action & Indications

- Competes with histamine at the **H1 site** on cells in the **respiratory tract** and **vasculature**. These agents do not prevent histamine release.
- Also has **anticholinergic** and **sedative** effects. Agents are divided into 1st and 2nd generations based on the incidence of sedation.
- Useful for **acute allergic reactions**, **allergic rhinitis**, and **motion sickness**.
- Also useful for **nausea/motion sickness**, **drug-induced extrapyramidal effects** and **Parkinson's disease**.

Common Dosages

- Diphenhydramine 25-50mg PO/IM/IV q4-6 hours, maximum 400mg/day
- Cetirizine 10mg PO daily

Adverse Effects & Contraindications

- **Sedation**, dizziness, drowsiness, confusion or delirium.
- **Urinary retention**, constipation or dry mouth.
- **Nausea**, **vomiting**, or diarrhea.
- **AVOID** use in **glaucoma** as it can increase intra-ocular pressure.
- Do **NOT** use with **monoamine oxidase inhibitors** (tranylcypromine, phenelzine) as it can lead to life-threatening interactions.

Practical Tips

- **Diphenhydramine** is **more sedating** than other antihistamines.
- **Additive effects can be seen when combined** with **alcohol** or **other sedating drugs**.
- Caution when **operating machinery or driving** while on antihistamines. Duration of drugs is usually 4-7 hours.
- **First generation anti-histamines** are preferred for **acute allergic reactions** due to a quicker onset of action and faster achievement of steady state concentrations.
- **Second generation anti-histamines** are preferred for the treatment of **season allergic rhinitis** as they are less sedating, and taken once daily.
- Second generation agents are **better tolerated** due to less drug crossing the blood brain barrier.
- Mostly hepatic metabolism with significant **first pass effect**.

"Remedies often worsen evil.... The wise physician knows when to prescribe and when not to, and sometimes it takes skill not to apply remedies.... There is no better remedy for disorder than to leave it alone to correct itself."

Gracián, Baltasar. The Art of Wordly Wisdom: A Pocket Oracle. 1647.

Alpha-Blockers

Drug Class: adrenergic α1 or α1a receptor blockers, urologics
Drugs: **alfuzosin** [Xatral], **doxazosin** [Cardura], **tamsulosin** [Flomax], **terazosin** [Hytrin]

Mechanism of Action & Indications

- α1 receptors are found on smooth muscle and cause contraction with sympathetic stimuli. Smooth muscle contraction of prostatic tissue around the urethra can impair urine flow. Blockade of these receptors will relax prostatic smooth muscle.
- Receptor subtypes α1a/1b/1d are found throughout the body. Approximately 75% of the prostate receptors are α1a, therefore, **1a selective agents** (tamsulosin, alfuzosin) may theoretically produce **fewer systemic side effects** by avoiding unnecessary blockade of systemic 1b/1d receptors.
- Use in symptomatic **benign prostatic hyperplasia**.
- Doxazosin, terazosin, and alfuzosin, but not tamsulosin, may be used as 4th line agents in **resistant hypertension**. Not used as first line agents in the treatment of hypertension as associated with fluid retention and heart failure (ALLHAT trial).

Common Dosages

- Alfuzosin 10mg PO daily
- Doxazosin 1-8 mg PO daily
- Tamsulosin 0.4-0.8 mg PO daily
- Terazosin 1-10mg PO daily-BID (maximum dose 20mg/day)

Adverse Effects

- Cardiovascular effects include **postural hypotension** and **syncope**, particularly upon administration of the initial dose. Give small initial test dose first, especially in the elderly.
- Can precipitate or worsen **congestive heart failure** (ALLHAT trial).
- Central nervous system effects include **fatigue** and **headache**.
- Genitourinary effects include **priaprism** and **retrograde ejaculation**.

Practical Tips

- Titration done every 2-6 weeks.
- Limited symptomatic gain with higher doses.
- Caution with **end stage renal failure** and with medications metabolized by cytochrome P450 3A4.
- Caution with other **anti-hypertensives**. For example, the use of α1 blockers may counteract the action of α1 agonists (e.g. clonidine).

"I would wish the young practitioner especially, to have deeply impressed on his mind, the real limits of his art, and that when the state of his patient gets beyond these, his office is to be a watchful, but quiet spectator of the operations of nature, giving them fair play by a well-regulated regimen, and by all the aid they can derive from the excitement of good spirits and hope in the patient."

Jefferson, Thomas. Letter to Dr. Casper Wistar, June 21, 1807.

APPENDIX

Unacceptable Abbreviations

No abbreviation in medication orders is acceptable. However, the following abbreviations have been particularly problematic and have lead to numerous documented medication errors and near misses.

Capital Health is targeting their communication and education strategy towards these particularly high-risk medication abbreviations. In the future, other problematic medication abbreviations will be added to this list and also included in targeted communication and education strategies.

Abbreviation	Intended Meaning	Misinterpretation	Correction
units	International Unit	Misread as IV (intravenous)	Use "unit"
U or u	Unit	Read as zero (0) or a four (4), causing a 10 fold overdose or greater (4U seen as "40" or 4u seen as "44")	"Unit" has no acceptable abbreviation. Use "unit"
q.d. or QD	Every day	Mistaken as q.i.d., especially if the period after the "q" or the tail of the "q" is misunderstood as an "i"	Use "daily" or "every day"
q.o.d. or Qdaily	Every other day	Mistaken as "q.d." (daily) or "q.i.d." (four times daily) if the "o" is poorly written	Use "every other day"
Zero after decimal point (1.0)	1 mg	Misread as 10 mg if the decimal point is not seen	Do not use terminal zeros for doses expressed in whole numbers
No zero before decimal dose (.5 mcg)	0.5 mcg	Misread as 5 mcg	Always use zero before a decimal when the dose is less than a whole unit.
Drug name abbreviations	Too numerous to list	Too numerous to list	Use the complete spelling for drug names

Adopted from: Institute for Safe Medication Practices
Preventing Medication Errors, November 2003
National Coordinating Council for Medication Error Reporting and Prevention © 1998 - 2003

Dangerous Abbreviations

Abbreviation	Intended Meaning	Misinterpretation	Correction
Apothecary symbols	Dram Minim	Misunderstood or misread (symbol for dram misread for "3" and minim misread as "mL")	Use the metric system
AU, AS, AD	Latin abbreviation for each ear, left ear, right ear	Mistaken for Latin abbreviation for OU (each eye), OS (left eye), daily (right eye)	Don't use these abbreviations. Write out "each ear", "left ear", "right ear"
BT	Bedtime	Mistaken as BID (twice daily)	Use "bedtime"
cc	Cubic centimeters	Misread as "U" (units)	Use "mL"
D/C	Discharge Discontinue	Premature discontinuation of medications when D/C (intended to mean "discharge") has been misinterpreted as "discontinued" when followed by a list of drugs	Use "discharge" and "discontinue"
o.d. or daily	Once daily	Misinterpreted as "right eye" (daily – oculus dexter) and administration of oral medications in the eye	Use "daily"
OU, OS, daily	Latin abbreviation for each eye, left eye, right eye	Mistaken for Latin abbreviation for AU (each ear), AS (left ear), AD (right ear)	Don't use these abbreviations. Write out "each eye", "left eye", "right eye"
Per os	Orally	The "os" can be mistaken for "left eye"	Use "PO", "by mouth", or "orally"
Q6PM, etc.	Every evening at 6 PM	Misread as every six hours	Use 6 PM "nightly"
Qhs	Bedtime	Misread as every hour	Use "bedtime"
qn	Nightly or at bedtime	Misinterpreted as "qh" (every hour)	Use "nightly"
SC	Subcutaneous	Mistaken for SL (sublingual)	Use "subcut." Or write "subcutaneous"
ss	Sliding scale (insulin) or ½ (apothecary) or side stream	Mistaken for "55"	Spell out "sliding scale", use "one-half" or "1/2" or use "side stream"
Sub q	Subcutaneous	The "q" has been mistaken for "every" (e.g., one heparin dose ordered "sub q 2 hours before surgery" misunderstood as every 2 hours before surgery)	Use "subcut.' or write subcutaneous
TIW or tiw	Three times a week	Mistaken as "three times a day"	Don't use this abbreviation
μg	Microgram	Mistaken for "mg" when handwritten	Use "mcg"
X 3d	For three days	Mistaken for "three doses"	Use "for three days"
> and <	Greater than and less than	Mistakenly used opposite of intended	Use "greater than" or "less than"
/ (slash mark)	Separates two doses or indicates "per"	Misunderstood as the number 1 ("25 unit/10 units" read as "110" units	Do not use a slash mark to separate doses. Use "per"
Name letters and dose numbers run together (e.g., Inderal40mg)	Inderal 40 mg	Misread as Inderal 140 mg	Always use space between drug name, dose, and unit of measure

Adopted from: Institute for Safe Medication Practices
Preventing Medication Errors, November 2003

Drugs that Require Triplicate Prescriptions in the Province of Alberta

PENTAZOCINE
Talwin

HYDROCODONE - DIHYDROCODEINONE
Caldomine Forte and Ped.
Calmydone
Coristex – DH
Coristine – DH
Dimetane Expct. – DC
Hycodan
Hycomine and Hycomine – S
Mercodol with Decapryn
Novahistex – DH and – DH Expct.
Novahistine – DH
Robidone
Triaminic Expct. – DH
Tussaminic – DH Forte and DH Pediatric
Tussionex

OXYCdallyONE
Endocet
Encodan
Oxycocet
Oxycodan
Percocet
Percocet - Demi
Percodan
Percodan - Demi
Supeudol

MORPHINE
Morphine Sulphate
- Morphine Sulphate
- MS Contin
- Morphine H.P. and L.P.
- Statex
- Epimorph
- MS-IR

Morphine Hydrochloride
- Morphitec
- Morphine Tincture
- M.O.S.
- M.O.S. S-R

OXYMORPHONE HYDROCLORIDE
Numorphan

FENTANYL/SUFENTANYL/ALFENTANYL
Sublimaze
Innovar
Duragesic (Patch)

METHADONE
*Note: May be prescribed only by those physicians authorized by H.P.B.

BUTALBITAL PREPS.
Fiorinal
Fiorinal C 1/4
Fiorinal C 1/2
Tecnal
Tecnal C 1/4
Tecnal C 1/2

HYDROMORPHONE-DIHYDROMORPHINONE
Dilaudid
Dilaudid - HP
Hydromorph Contin

NORMETHADONE -p- HYDROXYEPHEDRINE
Cophylac
Cophylac - Expct.

MEPERIDINE - PETHIDINE
Demerol
Pamergan

ANILERIDINE
Leritine

LEVORPHANOL TARTRATE
Levo-Dromoran

ANABOLIC STERIdallyS
Durabolin
Deca-Durabolin
Anapolon
Testosterone
Stanozolol
Winstrole
Does not include topical preparations or preparations such as Climacteron.

This list is provided for convenience only. It should not be viewed as an all inclusive of drugs included on the Triplicate Prescription Program.

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FEEDBACK

This version represents the second edition of Drugs & Drugs. The editorial committee welcomes any constructive feedback to help make this manual more practical, comprehensive, and user-friendly. Please send your comments to Dr. Peter Hamilton (peter.hamilton@ualberta.ca).

Suggestions for other commonly used drugs.

Suggestions for specific changes for individual drug(s).

Suggestions for format of this manual.

Suggestions for quotations in this manual.

Other suggestions.

Thank you!

DRUGS AND DRUGS

A PRACTICAL GUIDE TO THE SAFE USE OF COMMON DRUGS IN ADULTS

Remember how much you do not know. Do not pour strange medicines into your patients. - *William Osler*

One of the first duties of the physician is to educate the masses not to take medicines. *-William Osler*

Doctors pour drugs of which they know little, to cure diseases of which they know less, into human beings of whom they know nothing. *-Voltaire*

Polypharmacy is a prosthesis for the physician's incompetence. The less he knows, the more prescriptions he writes. *-Zeljko Poljak.*

The blind faith which some men have in medicines illustrates too often the greatest of all human capacities-the capacitiy for self-deception. *-William Osler*

The pen is deadlier than the scalpel--beware of things prescribed. *-Anon*

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